Premarket Approval Application (PMA) for Medtronic, Inc.’s Symplicity Spyral Radiofrequency Renal Denervation System

Circulatory System Devices Advisory Committee Meeting
August 23, 2023

Introduction, Background, Clinical Study Design

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Review Team

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Outline

- Introduction
- Background
- Device Description and Proposed Indications for Use
- Clinical Study Design
- Clinical Study Results
  - Safety
  - Effectiveness
- Patient preference study
- Post-approval Study
- Conclusions

Clinical Background

- Hypertension (HTN) is a major public health issue
  - Prevalence ~45% of US adults
  - Higher rate among African Americans (57.1%) vs. Caucasians (43.6%) & Hispanics (43.7%) (NHANES, 2017-2018)[1]
- Associated with increased risk of serious conditions including[2]
  - Stroke
  - Heart disease
  - Heart failure
  - Noncardiac vascular disease
  - Renal Disease
- BP medications are the mainstay of HTN therapy, but:
  - BP medication adherence in approximately 60% of patients[3]
  - Target BP achieved in approximately 45% of patients[4]

1. National Health and Nutrition Examination Survey Fact Sheet. *CDC*. July 2020. Available at: https://www.cdc.gov/nchs/data/factsheets/factsheet_nhanes.pdf
2. Carey RM et al. Prevention and Control of Hypertension: JACC Health Promotion Series. *J Am Coll Cardiol* 72(11). 2018.
3. Choudhry NK ea. Medication Adherence and Blood Pressure Control: A Scientific Statement From the American Heart Association. Hypertension. 2022;79:e1-e14
4. Dorans KS et al. Trends in prevalence and control of hypertension according to the 2017 ACC/AHA Guidelines. *J Am Heart Assoc* 7(11). 2018.

Defining Hypertension (1)

2017 US Societal Guideline Classification of Blood Pressure in Adults[5]

Category	SBP		DBP
Normal	<120 mmHg	AND	<80 mmHg
Elevated	120-129 mmHg	AND	<80 mmHg
Hypertension			
Stage 1	130-139 mmHg	OR	80-89 mmHg
Stage 2	≥140 mmHg	OR	≥90 mmHg

5. Whelton PK et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology / American Heart Association task force. *Circulation* 138(17). 2018.

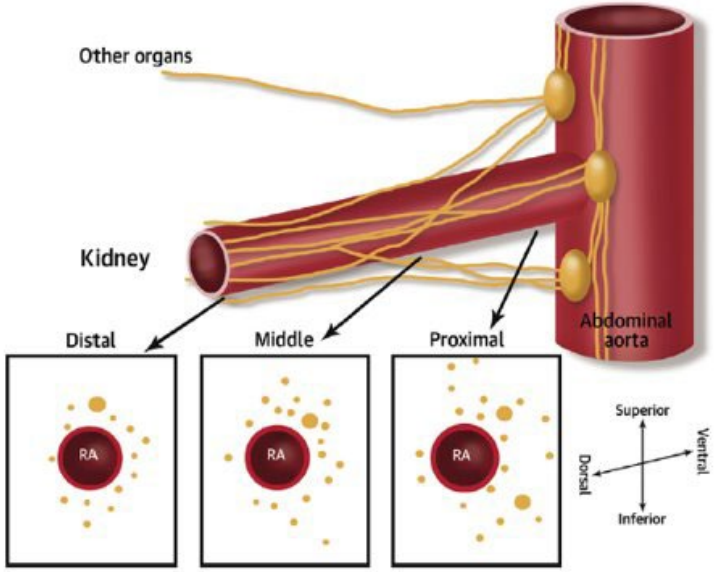
Defining Hypertension (2)

- Uncontrolled HTN: Above BP goal
  - Due to non-adherence to treatment; or
  - Despite adherence to treatment
- Resistant HTN: Above BP goal despite the use of 3 HTN medications (including a diuretic) with complementary mechanisms of action

Role of Renal Physiology in Hypertension

- Renal vasculature innervated by mainly efferent sympathetic nerves
- Stimulation of efferent nerves leading to:
  - Increased reabsorption of Na and water
  - Reduced renal blood flow and GFR (vasoconstriction)
  - Increased activity of the RAAS

Increased BP



Renal Denervation (RDN)

- Approach to reduce renal sympathetic activity by ablating the surrounding nerves
- Early single-arm clinical studies of percutaneous RDN technologies were promising with large magnitudes of BP reduction
- However, initial sham-controlled trials did not see quite as large BP reductions, and no difference between treatment and sham
- After denervation, some animal studies show re-innervation[6-8]
  - If re-innervation occurs in humans, sustained BP reduction could be impacted

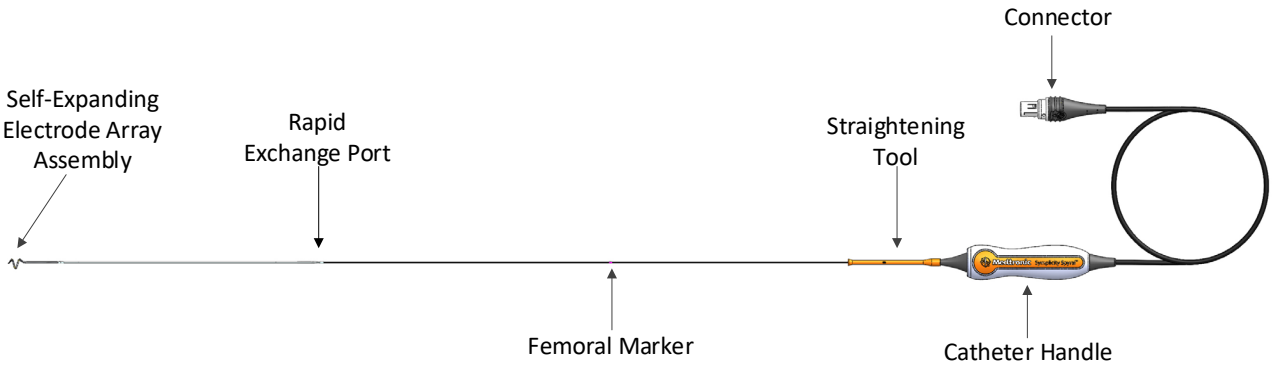
6. Mulder J et al. Renal sensory and sympathetic nerves reinnervate the kidney in a similar time-dependent fashion after renal denervation in rats. *Am J Physiol* 304(8). 2013.
7. Booth LC et al. Reinnervation following catheter-based radio-frequency renal denervation. *Exp Physiol* 100(5). 2015.
8. Kiuchi MG et al. Renal denervation update from the International Sympathetic Nervous System Summit: JACC State-of-the-Art Review. *J Am Coll Cardiol* 73(23). 2019.

2018 FDA Advisory Committee on HTN Devices

- Discussed clinical trial designs to evaluate safety and effectiveness of devices for HTN
- Key Panel recommendations[9]
  - Sham control trials
  - Trial designs
    - Medication withdrawal (off-med) study
    - Standardized BP medication (on-standardized med) study
  - Ambulatory BP measurement (ABPM) used as the primary BP assessment method
  - A 5-7 mmHg difference in BP reduction between active treatment and sham is clinically significant
  - Patient preference information is of value

9. December 2018 Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting on Clinical Evaluation of Anti-Hypertensive Devices. bit.ly/3OEirtN

Symplicity Spyral Radiofrequency Renal Denervation (rfRDN) System



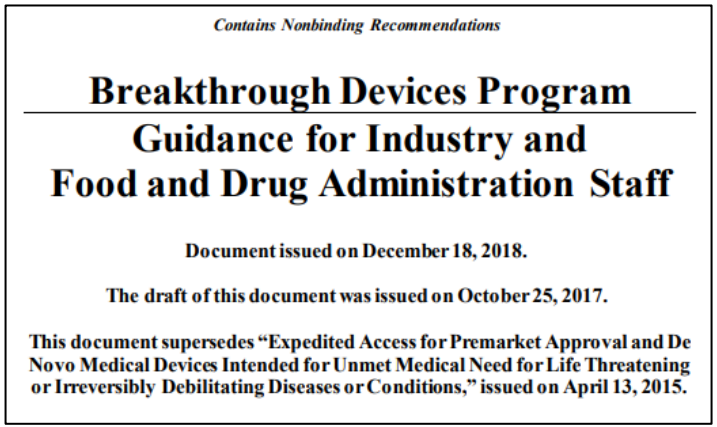
Symplicity Spyral rfRDN System

Proposed indications for use:

The Symplicity Spyral multi-electrode renal denervation catheter and the Symplicity G3™ RF Generator are indicated for the reduction of blood pressure in patients with *uncontrolled hypertension despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated*.

Breakthrough Devices Program (1)

- Symplicity Spyral granted breakthrough status in March 2020 for patients with uncontrolled hypertension
- Breakthrough Devices may provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions
- Intended to provide patients with timely access to certain devices by expediting their development, assessment, and review



Contains Nonbinding Recommendations

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2018.

The draft of this document was issued on October 25, 2017.

This document supersedes "Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions," issued on April 13, 2015.

10. FDA Guidance. Breakthrough Devices Program. December 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

Breakthrough Devices Program (2)

- **Does** allow for:
  - Interactive and timely communication with FDA
  - Prioritized review of submissions
  - Efficient and flexible clinical study design
  - Expedited review of preapproval manufacturing and quality systems compliance
  - Pre/Postmarket balance of data collection
- **Does not** alter/reduce the statutory requirement for premarket approval: reasonable assurance of safety and effectiveness

10. FDA Guidance. Breakthrough Devices Program https://www.fda.gov/media/108135/download

Pre/Postmarket Balance of Data Collection

- FDA may accept greater uncertainty for a premarket submission along with timely postmarket data collection if the uncertainty is sufficiently balanced
- Benefit/Risk considerations include:
  - Probable benefits from earlier access

    vs.
  - Probable risk of harm should postmarket data show that the device is ineffective or unsafe

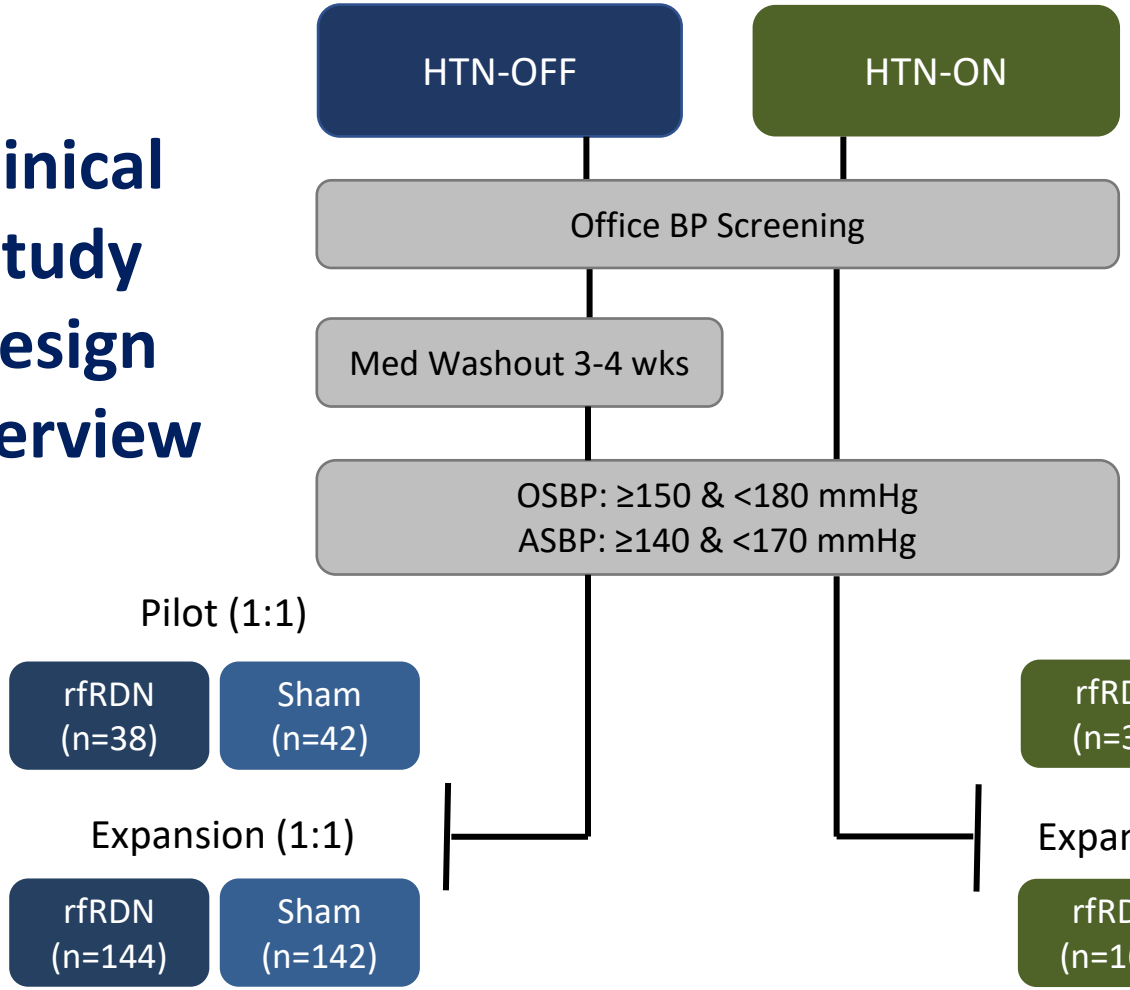
Nonclinical and Preclinical Device Evaluation

- Catheter Engineering Testing
  - Bench testing
  - Energy output and delivery
- Generator Engineering Testing
  - Electrical safety
  - Software validation
  - Cybersecurity
- System Compatibility
- Biocompatibility
- Sterilization & Packaging
- Preclinical Animal Studies

No outstanding non-clinical study issues

CLINICAL STUDY DESIGN

Clinical Study Design Overview



Medication Escalation

- **HTN-OFF: Between 3-6 months to goal (<140 mmHg OSBP)**

Unblinding & Crossover

- **Pilot Cohorts: 12 months**
- **Expansion Cohorts: 6 months**

Key Enrollment Criteria

	HTN-OFF	HTN-ON
Age	≥20 and ≤80 years old at time of enrollment (consent).	
OBP	OSBP ≥150 mmHg and <180 mmHg and ODBP ≥90 mmHg	
ABP	24-hour SBP ≥140 mmHg and <170 mmHg	
Medications	Willing to discontinue antihypertensive medications at screening Visit 1 through the 3-month post-procedure visit	• On 1-3 antihypertensive medications at ≥50% maximal dose • Stable medication regimen for ≥6 weeks

OBP/ABP = Office/ambulatory blood pressure

Follow-up Schedule

	Screening	Baseline	Procedure	1M	3M	6M	12M	24-36M
OBPM	x	x		x	x	x	x	x
ABPM		x			x	x	x	x
Duplex Ultrasound						x	x	
CTA/MRA						x[1]	x[2]	
Drug testing		x			x	x	x	x
Blood chemistry		x		x	x	x	x	x
Quality of Life		x			x	x	x	x
Blinding assessment			discharge		x	x		

OBPM/ABPM: Office/ambulatory blood pressure measurement; CTA: computed tomography angiography; MRA: magnetic resonance angiography

[1]Required if renal artery stenosis suspected

[2]Required for at least 150 subjects or if renal artery stenosis suspected

Statistical Analysis Plan

Adrijo Chakraborty, PhD
Statistician
Office of Clinical Evidence and Analysis

Study and Analysis Cohorts

	HTN-OFF	HTN-ON
Pilot Cohort: Subjects enrolled in the Pilot study	80	80
Expansion Cohort: Subjects enrolled following Pilot study	251	257
Additional subjects enrolled following positive interim analysis	35	--
Primary (Bayesian) Cohort: Expansion + discounted Pilot	Up to 331 Based on Bayesian analysis	Up to 337 Based on Bayesian analysis
Full Cohort: All enrolled subjects	366	337

Primary Safety Endpoint

The primary safety endpoint was defined as the occurrence of at least one of the following major adverse events (MAE):

a. 30 days

- All-cause mortality
- End stage renal disease
- Significant embolic events resulting in end-organ damage
- Renal artery perforation requiring intervention
- Renal artery dissection requiring intervention
- Major vascular complications
- Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol

b. New renal artery stenosis (RAS), defined as a >70% diameter stenosis, confirmed by renal angiography at 6 months as determined by angiographic core laboratory

Primary Safety Endpoint

Statistics Hypothesis and Analysis

- Analysis population: First 253 evaluable RDN-treated subjects from the SPYRAL HTN-OFF and SPYRAL HTN-ON
- Safety event rate performance goal (PG) = 7.1% derived from literature review
- The primary safety null and alternative hypotheses:

$$H_0: \pi \geq 7.1\%$$

$$H_a: \pi < 7.1\%$$

where π is the proportion of subjects who had experience at least one of the safety endpoint event

- Exact binomial test
- Level of significance (one-sided) 0.05

Additional analyses for pooled Pilot and Expansion Cohorts

Primary Effectiveness Endpoint

HTN-OFF: Change in SBP from baseline to 3-months post-procedure measured by 24-hour ABPM

HTN-ON: Change in SBP from baseline to 6-months post-procedure measured by 24-hour ABPM

- **Primary effectiveness endpoint evaluated for each trial individually**
- **Intent to treat population used for the effectiveness assessment**
- **Baseline BP used as a covariate in the statistical model to derive the treatment effect**

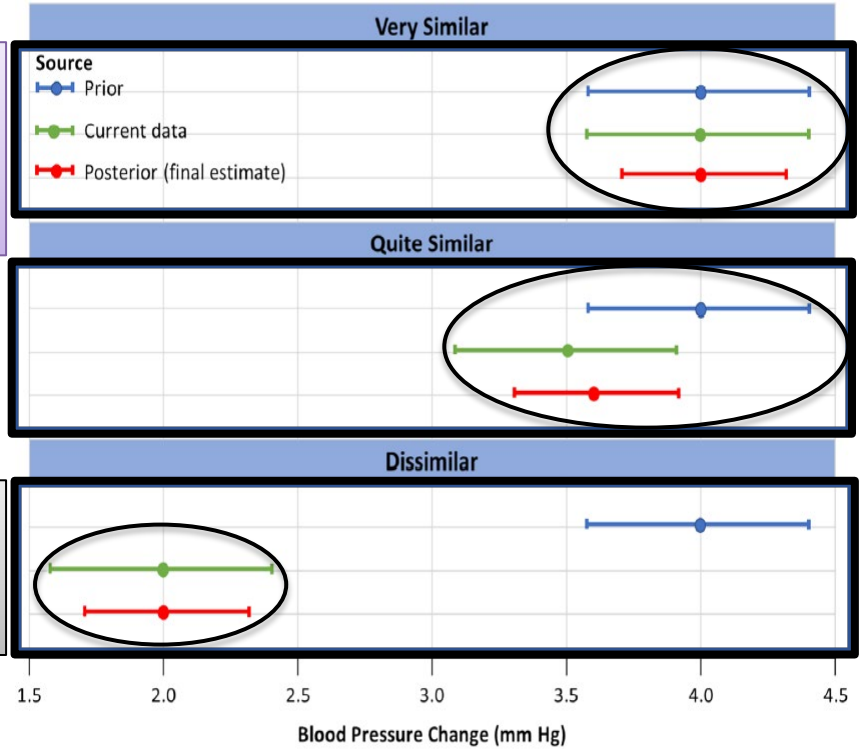
Effectiveness Endpoint Analysis

Power Prior based on similarity of outcomes

- Informative priors for the unknown parameters (such as ASBP change at follow-up) were developed from the Pilot study data
- The amount of information used from the pilot was based on the similarity between the effectiveness endpoint results of the Pilot and Expansion cohorts
- Amount of information to be used from the Pilot was determined separately for treatment and control arms

Greater similarity between Pilot and Expansion outcomes => more Pilot information is used

Lesser similarity between Pilot and Expansion outcomes => less Pilot information is used



11. Bohm M ea. Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal) and presence (SPYRAL HTN-ON MED Expansion) of antihypertensive medicat. 2020;109(5):289-302.

Primary Effectiveness Endpoint

Statistical Analysis

Let $\mu = \mu_t - \mu_c$ represents the treatment effect of BP change comparing treatment (RDN) and control (sham) groups where μ_t and μ_c are the BP changes in the treatment and control groups, respectively, at 3 months for HTN-OFF and 6 months for HTN-ON. The hypotheses are:

$$H_0: \mu \geq 0 \text{ vs.}$$

$$H_a: \mu < 0$$

- Interim analyses performed
- Informative prior developed from the Pilot Cohort using the Power Prior method
- Baseline BP used as a covariate in the statistical model to derive the treatment effect estimate
- Null hypothesis rejected if the posterior probability of H_a >0.975, the prespecified threshold for success

Primary Effectiveness Endpoint

Interim Analysis

Bayesian design with interim analyses

- HTN-OFF:
  - Planned when 210, 240 evaluable subjects are available (maximum study size 300)
  - Enrollment was stopped after the first interim analysis
- HTN-ON:
  - Planned when 110, 149 evaluable subjects available to determine if the enrollment could be stopped (maximum study size 260)
  - Enrollment continued to full enrollment (257 subjects)

Primary Effectiveness Endpoint

Statistical Analysis

- Considerations with the proposed approach
  - Amounts of pilot data leveraged for treatment and control were different
  - Use outcome data to determine similarity of the Pilot and Expansion data
  - Amounts of pilot data leveraged may vary at each interim analysis or the final analysis
- To study the robustness of results based on the proposed approach, several sensitivity analyses were conducted.
- As a secondary analysis of the primary effectiveness endpoints, ANCOVA method was used to determine the baseline adjusted treatment effect estimate.

Secondary and Additional Effectiveness Endpoints

Secondary endpoints

- Change in office SBP from baseline
- Change in office and ambulatory DBP from baseline
- Proportion of subjects achieving target OSBP (<140 mmHg)

Additional endpoints

- Medication burden assessed using Medication Index methodologies

Statistical analysis considerations

- Bayesian analyses only performed to evaluate change in Office SBP (HTN-OFF and HTN-ON)
- The results of the secondary endpoint assessment may not be interpretable if the primary endpoint is not met
- No prespecified plan for multiplicity adjustment to control for overall type 1 error rate

Subgroup Analysis of the Primary Effectiveness Endpoint

- Prespecified subgroup analyses conducted for several subgroups including gender, race/ethnicity, and geography (US vs. non-US subjects), without multiplicity adjustment
- Entire pilot and Expansion datasets combined and analyzed

Clinical Study Results

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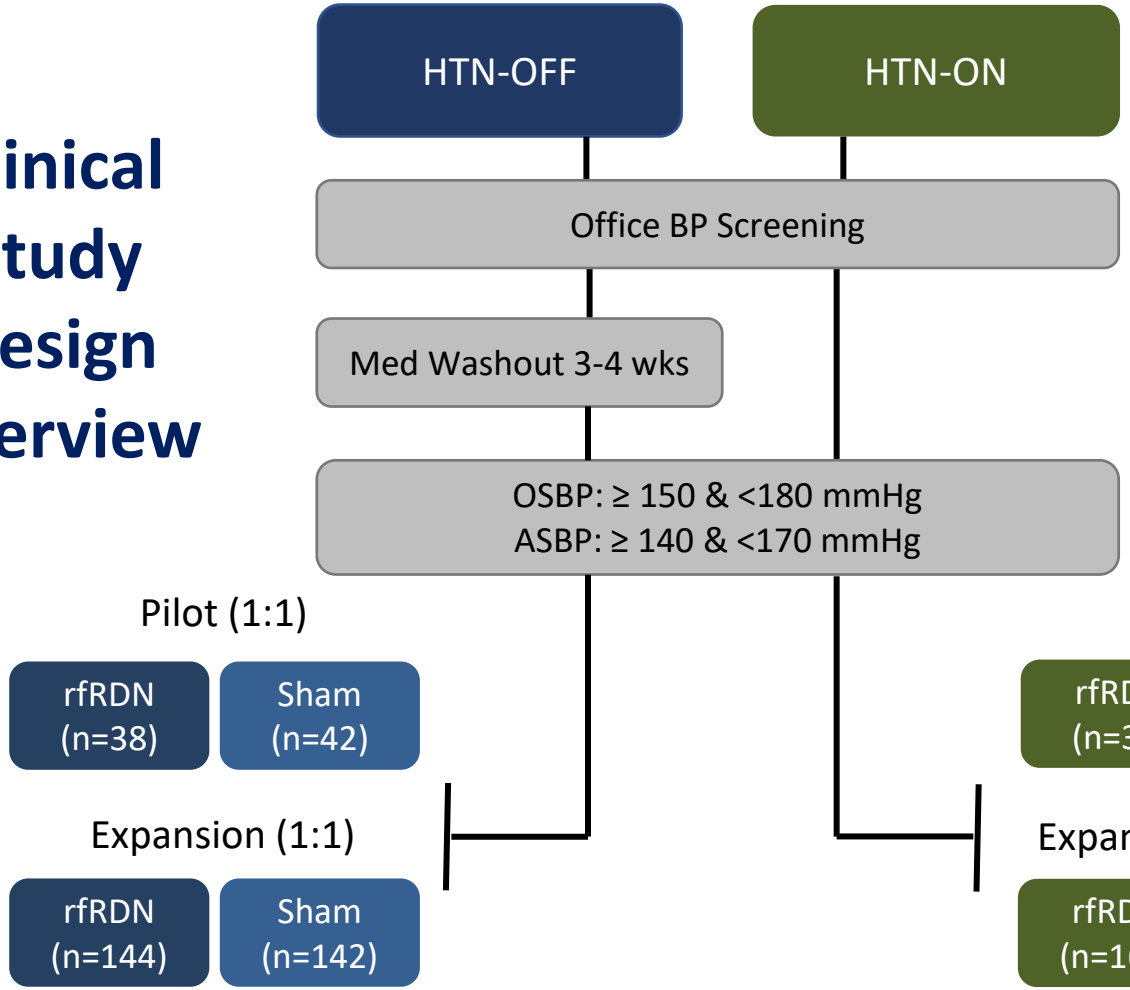
Cardiologist
Office of Cardiovascular Devices

Clinical Study Design Overview



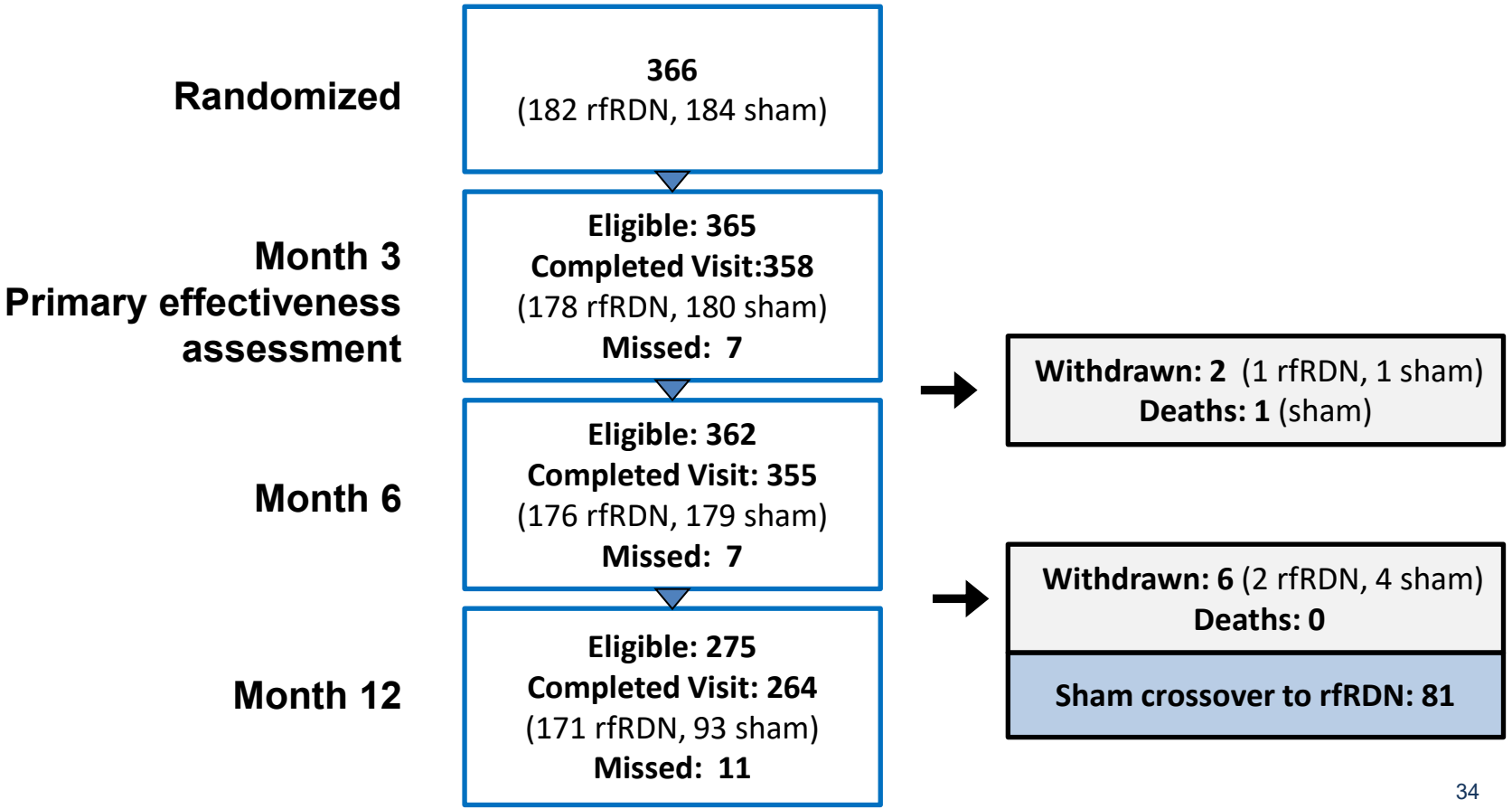
Medication Escalation

- **HTN-OFF: Between 3-6 months to goal (<140 mmHg OSBP)**

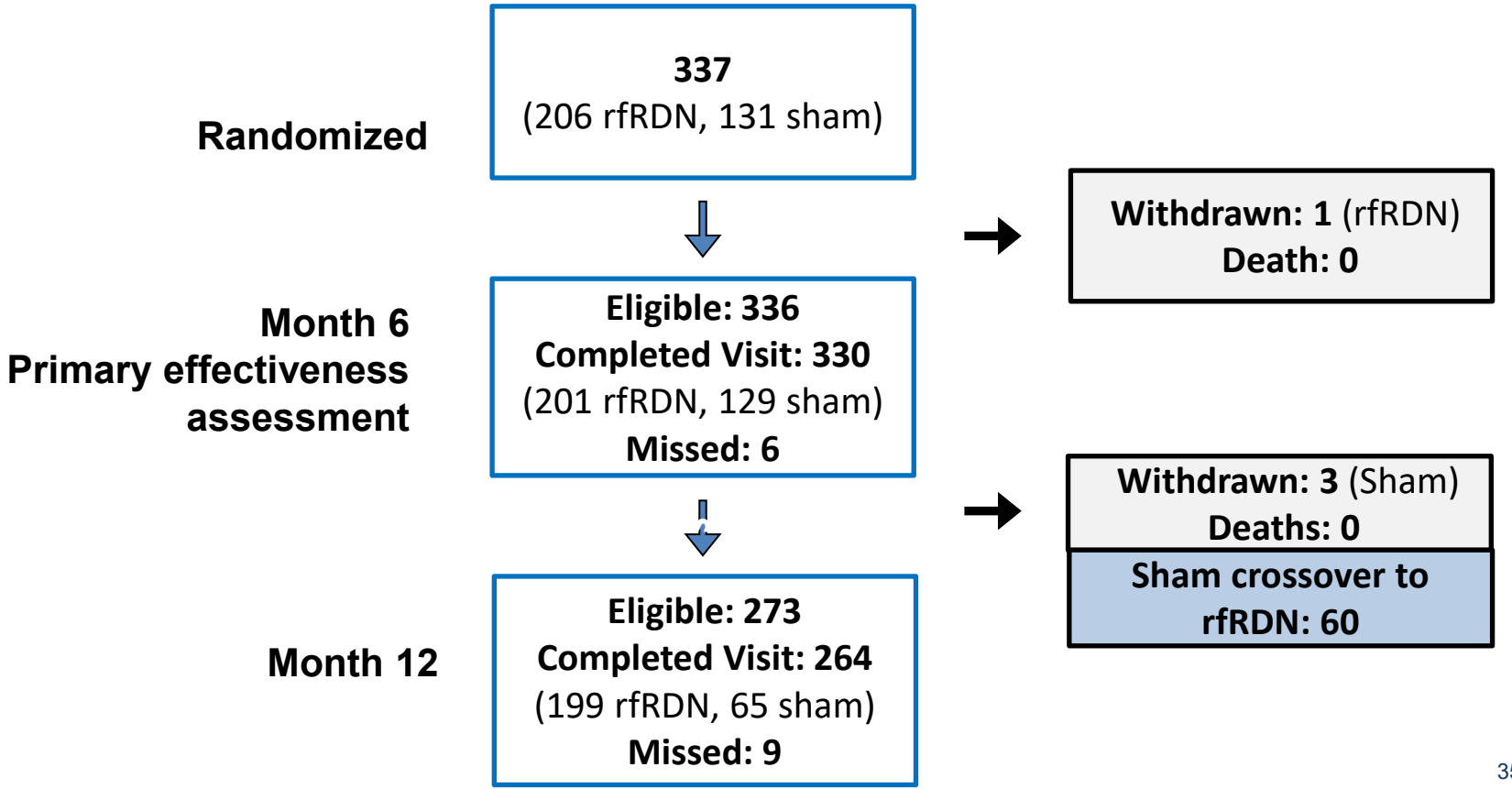
Unblinding & Crossover

- **Pilot Cohorts: 12 months**
- **Expansion Cohorts: 6 months**

HTN-OFF Subject Accountability



HTN-ON Subject Accountability



HTN-OFF Blinding Assessment

	Patient Blinding Index[1] (95% CI)	BP Assessor Index[1]
Discharge	0.66 (0.61, 0.71)	0.82 (0.78, 0.86)
3-Months	0.53 (0.48, 0.59)	0.73 (0.68, 0.78)
1 Blinding Index: 1= complete blinding, 0=complete unblinding, 0.5=random guessing		

Subject blinding was effective and was comparable between rfRDN and Sham subjects

HTN-ON Blinding Assessment

	Patient Blinding Index1 (95% CI)	BP Assessor Index
Discharge	0.68 (0.63, 0.73)	0.82 (0.78, 0.87)
3-Months	0.58 (0.53, 0.63)	0.75 (0.70, 0.79)
6-Months	0.58 (0.53, 0.63)	0.73 (0.68, 0.78)
1 Blinding Index: 1= complete blinding, 0=complete unblinding, 0.5=random guessing		

Subject blinding was effective and was comparable between rfRDN and Sham subjects

HTN-OFF Select Baseline Characteristics

Subject Baseline Characteristic	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
	rfRDN (N=38 Subjects)	Sham (N=42 Subjects)	rfRDN (N= 128 Subjects)	Sham (N= 123 Subjects)	rfRDN (N=182 Subjects)	Sham (N=184 Subjects)
Age (yrs)	55.8 ± 10.1	52.8 ± 11.5	51.4 ± 10.9	52.5 ± 10.0	52.5 ± 10.8	52.7 ± 10.1
Male	68.4%	73.8%	63.3%	66.7%	64.3%	69.6%
Length of hypertension diagnosis >5 yrs	60.5%	42.9%	53.9%	58.5%	56.1%	56.0%
Geography						
US	34.2%	34.2%	55.5%	52.8%	50%	46.2%
OUS	64.8%	64.8%	44.5%	47.2%	50%	53.8%
Race						
White	26.3%	23.8%	28.9%	32.5%	30.8%	32.6%
Black or African American	13.2%	11.9%	24.2%	21.1%	20.3%	17.4%
Asian	2.6%	2.4%	3.9%	0.8%	3.8%	1.1%
Japanese from Japan	5.3%	4.8%	0.8%	0.0%	1.6%	1.1%
Not reportable per local laws or regulations	52.6%	57.1%	41.4%	44.7%	42.9%	47.3%
Other	0.0%	0.0%	0.8%	0.8%	0.5%	0.5%

HTN-OFF Baseline Blood Pressure

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
Baseline Blood Pressure (mmHg)	**rfRDN (N=38)**	**Sham (N=42)**	**rfRDN (N=128)**	**Sham (N= 123)**	**rfRDN (N=182)**	**Sham (N=184)**
Office measurements						
Systolic blood pressure	162.0 ± 7.6	161.4 ± 6.4	162.9 ± 7.9	163.4 ± 7.8	162.8 ± 7.8	163.2 ± 7.7
Diastolic blood pressure	99.9 ± 6.8	101.5 ± 7.5	101.6 ± 7.0	102.2 ± 7.0	101.1 ± 7.1	102.2 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	153.4 ± 9.0	151.6 ± 7.4	150.8 ± 7.7	150.8 ± 7.5	151.2 ± 7.9	151.3 ± 7.6
Mean diastolic blood pressure	99.1 ± 7.7	98.7 ± 8.2	97.6 ± 7.7	99.2 ± 7.2	97.6 ± 7.9	99.3 ± 7.5

HTN-ON Select Baseline Characteristics

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion)	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Sham (N=42 Subjects)**	**rfRDN (N=168 Subjects)**	**Sham (N=89 Subjects)**	**rfRDN (N=206 Subjects)**	**Sham (N=131 Subjects)**
Age (yrs)	53.9 ± 8.7	53.0 ± 10.7	55.5 ± 9.0	55.4 ± 8.7	55.2 ± 9.0	54.6 ± 9.4
Male	86.8%	81.0%	79.8%	77.5%	81.1%	78.6%
Length of hypertension diagnosis >5 yrs	60.5%	81.0%	72.1%	82.0%	69.9%	81.7%
Geography						
US	39.5%	42.9%	45.2%	52.8%	44.2%	49.6%
OUS	60.5%	57.1%	54.8%	47.2%	55.8%	50.4%
Race						
White	34.2%	35.7%	34.5%	37.1%	34.5%	36.6%
Black or African American	10.5%	11.9%	18.5%	22.5%	17.0%	19.1%
Asian	0.0%	2.4%	1.2%	3.4%	1.0%	3.1%
Japanese from Japan	7.9%	2.4%	7.1%	5.6%	7.3%	4.6%
Not reportable per local laws or regulations	47.4%	47.6%	36.9%	29.2%	38.8%	35.1%
Other	0.0%	0.0%	0.0%	1.1%	0.0%	0.8%

HTN-ON: Baseline Blood Pressure

Subject Baseline Blood Pressure (mmHg)	Pilot Cohort		Expansion Cohort		Full Cohort	
	rfRDN (N=38 Subjects)	Control (N=42 Subjects)	rfRDN (N=168 Subjects)	Control (N=89 Subjects)	rfRDN (N=206 Subjects)	Control (N=131 Subjects)
Office measurements						
Systolic blood pressure	164.4 ± 7.0	163.5 ± 7.5	162.6 ± 7.8	162.9 ± 8.2	163.0 ± 7.7	163.1 ± 7.9
Diastolic blood pressure	99.5 ± 6.9	102.7 ± 8.0	101.5 ± 6.9	100.9 ± 6.9	101.2 ± 7.0	101.5 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	152.1 ± 7.0	151.3 ± 6.8	149.0 ± 6.8	148.3 ± 6.9	149.6 ± 7.0	149.3 ± 7.0
Mean diastolic blood pressure	97.2 ± 6.9	97.9 ± 8.4	96.5 ± 7.7	94.6 ± 7.2	96.6 ± 7.6	95.7 ± 7.7

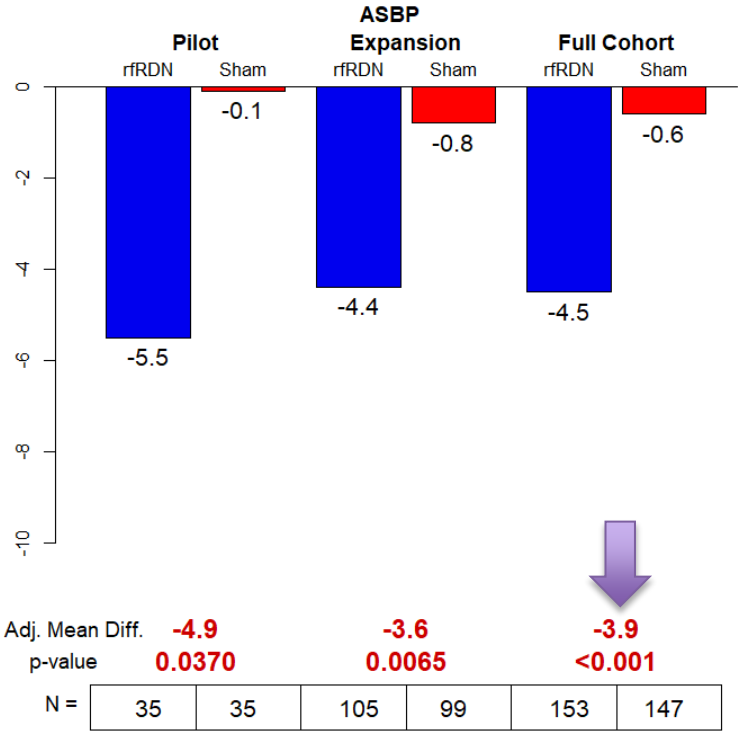
rfRDN Procedural Characteristics

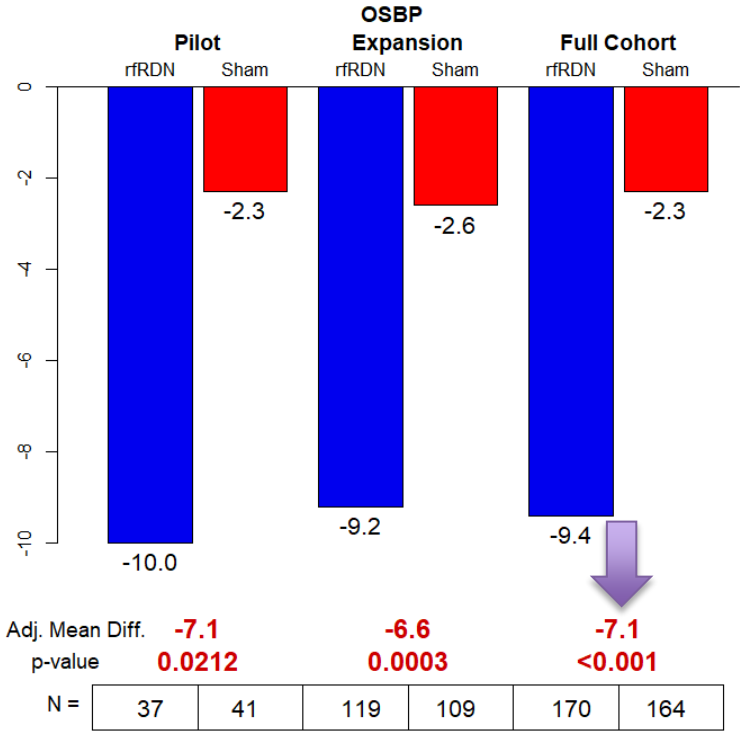
rfRDN Subjects	HTN-OFF N=182	HTN-ON N=206
Procedure Time (min)	99.3 ± 36.2	91.3 ± 31.2
Denervation Time (min)	59.7 ± 24.3	54.4 ± 19.2
Amount of Contrast used (cc)	207.8 ± 96.1	204.2 ± 81.4
Intra-procedural medication		
Pain meds	29.7% (54/182)	21.8% (45/206)
Sedatives/Anxiolytics	100.0% (182/182)	98.5% (203/206)
Atropine	2.2% (4/182)	2.9% (6/206)
Hospital Stay (days)	1.0 ± 0.1	1.0 ± 0.2
Device success	100.0% (181/181)	100.0% (205/205)
Procedure success	100.0% (181/181)	99.5% (204/205)

HTN-OFF EFFECTIVENESS RESULTS

HTN-OFF ASBP & OSBP Results at 3 Months

Pilot, Expansion, and Full Cohort Frequentist Analysis





p-values not adjusted for multiplicity

SBP changes are unadjusted reductions from baseline

Differences and p-values determined from ANCOVA models adjusting for the baseline value

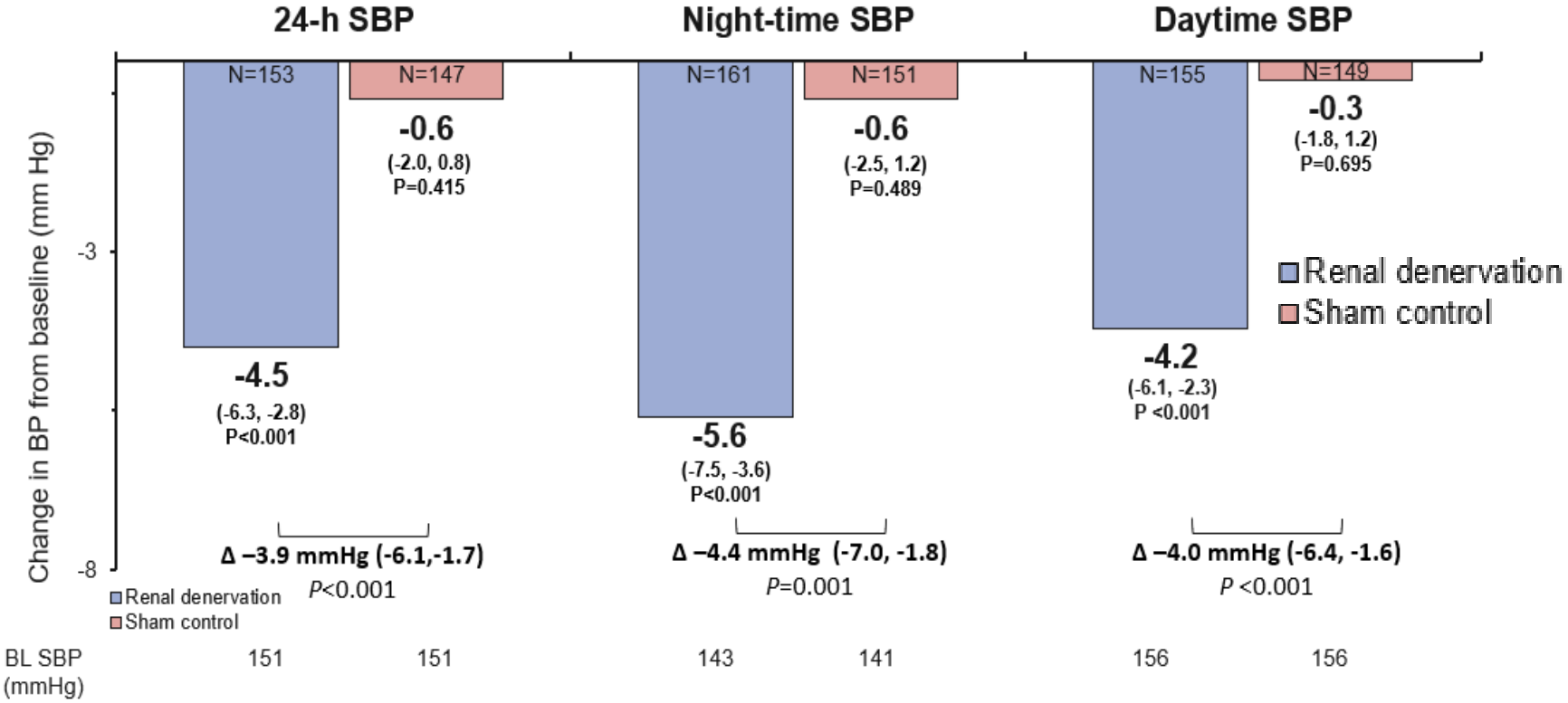
HTN-OFF Primary and Powered Secondary Effectiveness Endpoint

Bayesian Analysis at 3 Months

	Pilot Cohort sample size (evaluable)	Effective Pilot Cohort sample size after discounting	α-discount parameter Estimate	Expansion Cohort sample size	Bayesian estimate of treatment effect (95% BCI)	Posterior probability of success (>0.975 meets success criteria)
Primary Endpoint: 24-hour ASBP @ 3 months						
rfRDN	35	30	0.864	105	-3.9 mmHg (-6.2 to -1.6)	0.9996
Sham	35	34	0.967	99		
Secondary Endpoint: Office SBP @ 3 months						
rfRDN	37	36	0.980	119	-6.5 mmHg (-9.6 to -3.5)	1.000
Sham	41	41	0.998	109		

HTN-OFF Daytime vs. Nighttime ASBP at 3 Months

Full Cohort

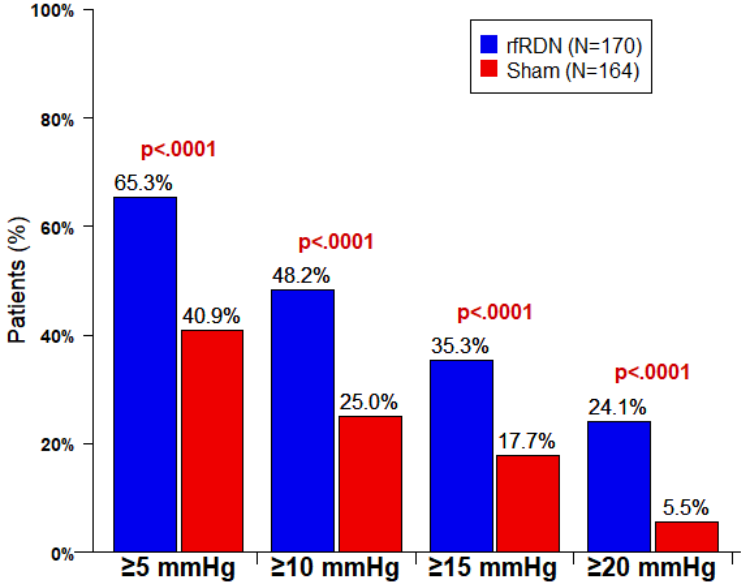


p-values not adjusted for multiplicity. SBP changes are unadjusted reductions from baseline
Differences and p-values determined from ANCOVA models adjusting for the baseline value

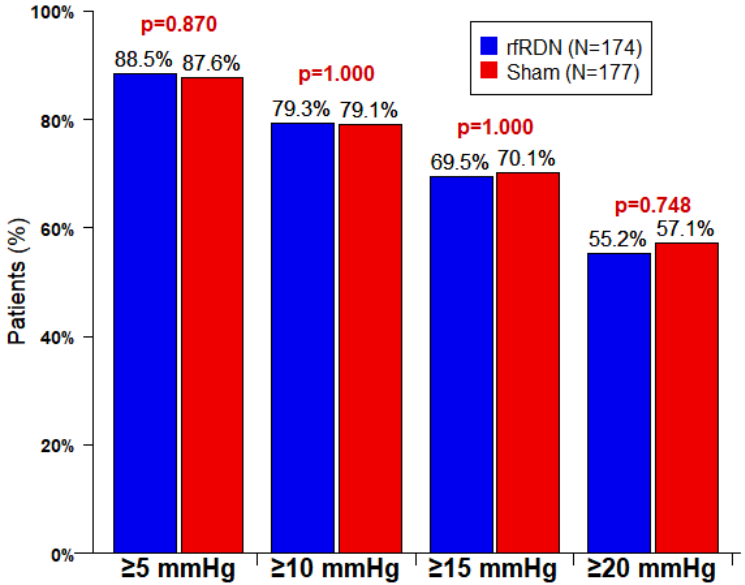
HTN-OFF Office SBP Changes at 3 and 6 Months

Full Cohort

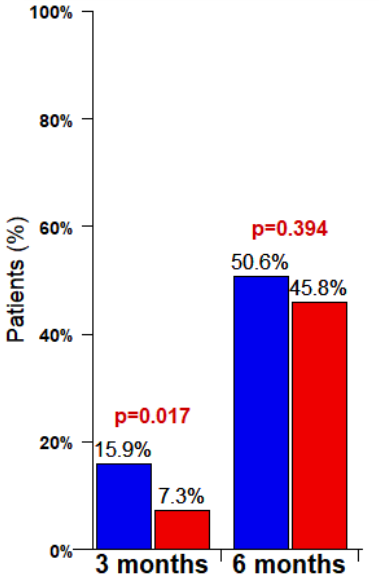
OSBP at 3 months



OSBP at 6 months



Subjects at target (<140 mmHg)



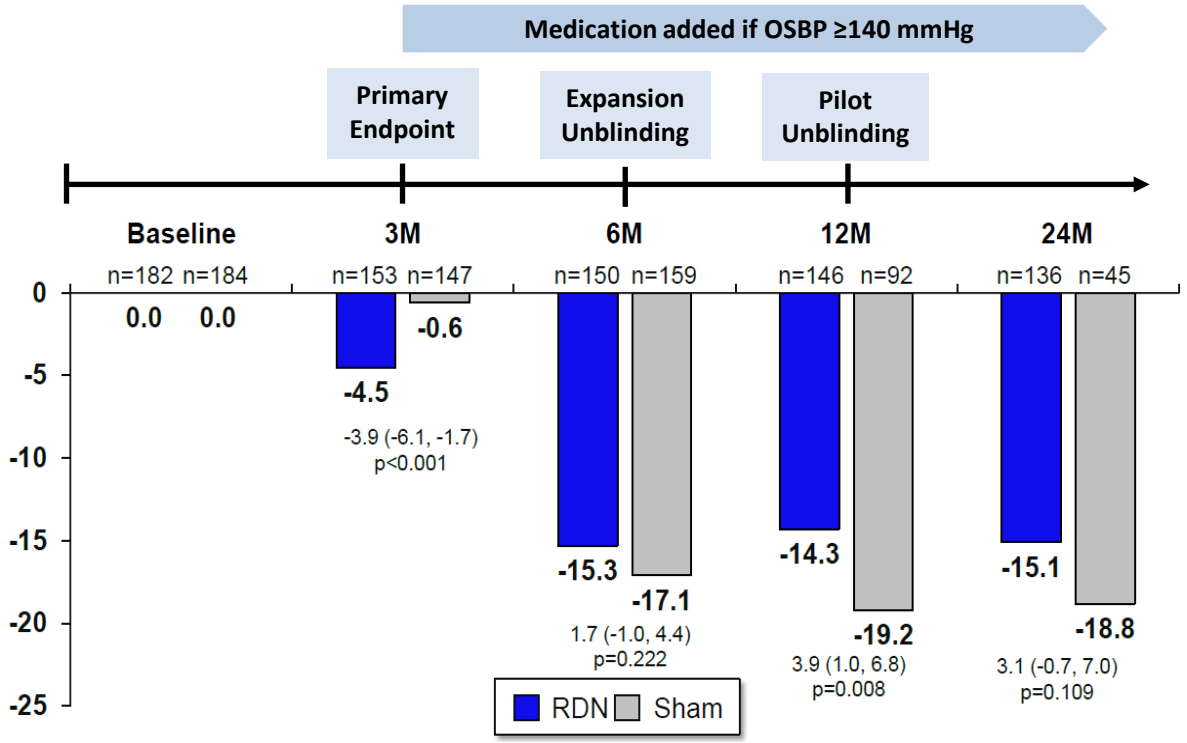
Attenuation of OSBP difference at 6 months

p-values not adjusted for multiplicity

HTN-OFF Durability of BP Reduction

- 3.9 mmHg BP reduction difference in favor of rfRDN statistically significant at 3-months
- Not maintained at 6, 12, and 24 months
- BP meds added
- Unblinding between 6 and 12 months
- Smaller numbers in Sham group at 12 and 24 months due to crossovers

24-hr ASBP change – Full Cohort



p-values not adjusted for multiplicity
SBP changes are unadjusted reductions from baseline
Differences and p-values determined from ANCOVA models adjusting for the baseline value

Medication Burden - *Medication Index 1*

- Medication Index 1 $(\mathrm{MedIndex1, MI1}) = \sum_{AH\ Meds} \left(\frac{prescribed\ dose}{maximum\ standard\ dose} \right)$
- MI1 corresponds to the number of maximum standard doses
- Example: For a patient taking 3 meds:
  - One med at max dose
  - One med at ½ max dose
  - One med at ¼ max dose

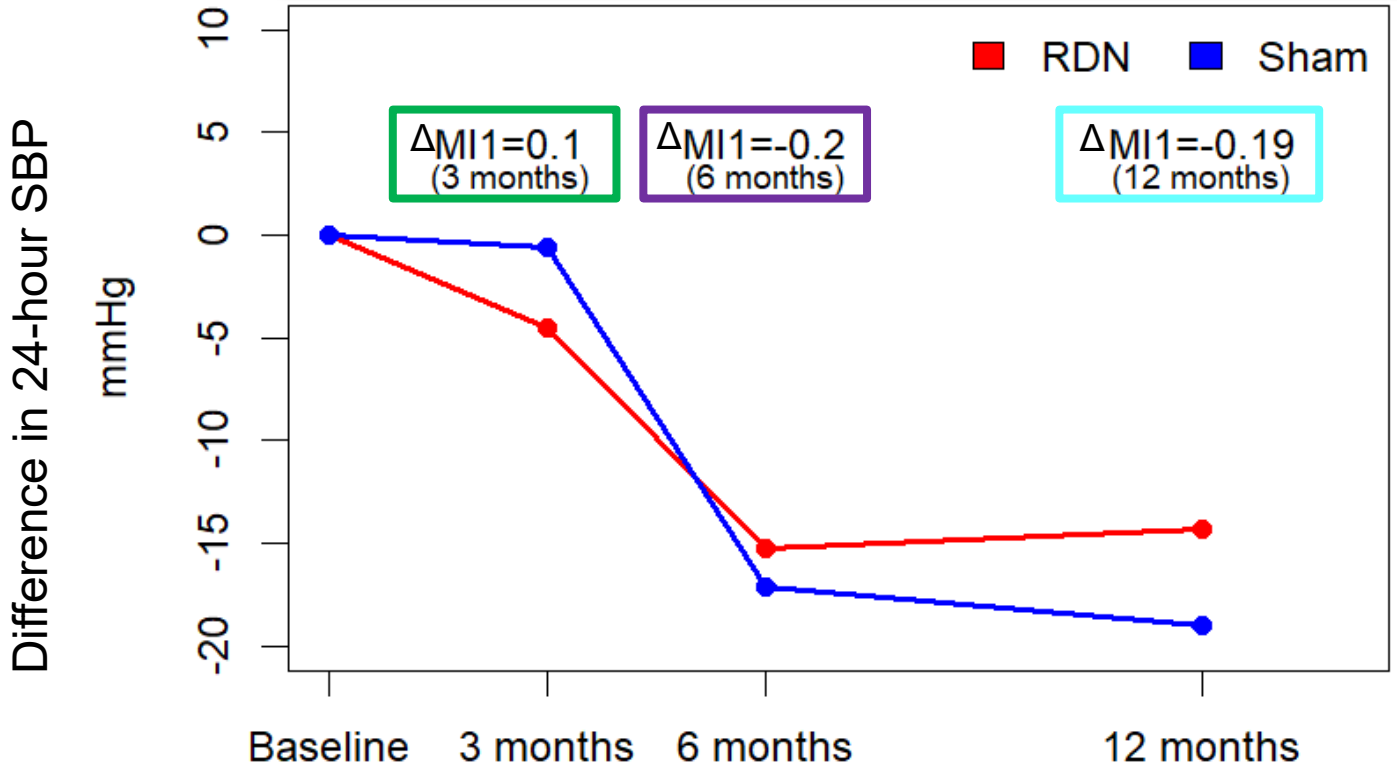
  MI1 = 1.75
- Average MI1 for a population = the average number of maximum standard doses meds
- Analysis
  - Calculate the average change in MI1 from baseline to follow-up
  - Relative MI1 change = the difference of the average change between treatment groups

Example: A relative MI1 change of -1.5 corresponds to the sham group, on average, increasing meds vs. baseline by 1.5 full med doses vs. the RDN group

HTN-OFF Durability of ASBP Reduction

Changes in 24-hour ABP and MI1 Compared to Baseline – Full Cohort

ΔMI1 = Δ in RDN MI1 - Δ in Sham MI1



HTN-OFF Subgroup Analysis – Full Cohort

Reduction in 24-hour SBP at 3 Months

	N	Adjusted treatment difference (95% CI)	Interaction p-value
Age			
< 65 years	270	-3.6 (-5.9, -1.3)	0.41
≥ 65 years	30	-6.8 (-14.1, 0.6)	
Sex			
Female	95	-2.3 (-6.4, 1.8)	0.33
Male	205	-4.7 (-7.3, -2.1)	
BMI			
Tertile 1 (BMI < 28.2)	104	-3.9 (-7.5, -0.2)	0.94
Tertile 2 (28.2 ≤ BMI < 32.3)	102	-4.4 (-8.0, -0.8)	
Tertile 3 (BMI ≥ 32.3)	94	-3.3 (-7.8, 1.1)	
Diabetes			
Yes	7	-6.0 (-32.3, 20.3)	0.80
No	293	-3.8 (-6.0, -1.6)	
Smoking			
Current	49	-5.3 (-11.2, 0.6)	0.39
Former	84	-1.6 (-6.0, 2.8)	
Never	167	-4.7 (-7.6, -1.9)	
Obstructive sleep apnea			
Yes	23	-5.9 (-17.5, 5.7)	0.63
No	277	-3.8 (-6.0, -1.5)	
AH Med Compliance at Baseline and 3M			
Yes	258	-3.8 (-6.1, -1.5)	0.96
No	31	-3.8 (-13.1, 5.5)	
Geography			
US	141	-2.7 (-5.8, 0.5)	0.40
OUS	159	-4.7 (-7.7, -1.6)	

-40 -30 -20 -10 0 10 20

Treatment difference (mmHg)

	N	Adjusted treatment difference (95% CI)	Interaction p-value
Orthostatic hypertension			
Yes	109	-6.5 (-10.5, -2.5)	0.07
No	185	-2.5 (-5.2, 0.1)	
Orthostatic Tachycardia			
Yes	119	-6.1 (-9.8, -2.4)	0.14
No	175	-2.8 (-5.6, -0.1)	
Race			
US African-American	49	-1.7 (-6.1, 2.7)	0.66
US Non-African-American	92	-3.2 (-7.6, 1.2)	
Renal function			
eGFR < 60	12	0.2 (-18.7, 19.0)	0.48
eGFR ≥ 60	288	-4.1 (-6.3, -1.8)	
Baseline ARR			
Tertile 1 (<5.39)	88	-6.17 [-10.26, -2.07]	0.13
Tertile 2 (5.39 to 12.16)	96	-4.51 [-8.23, -0.78]	
Tertile 3 (≥12.16)	87	-0.60 [-4.71, 3.51]	
Baseline Aldosterone			
Tertile 1 (<6)	98	-4.67 [-8.69, -0.66]	0.92
Tertile 2 (6 to 10)	98	-4.07 [-8.00, -0.13]	
Tertile 3 (≥10)	89	-3.57 [-7.62, 0.48]	
Plasma Renin Activity			
< 0.65	138	-1.51 [-4.79, 1.76]	0.09
≥ 0.65	137	-5.49 [-8.72, -2.26]	
24h Pulse Pressure (mmHg)			
< 60	253	-4.2 (-6.6, -1.7)	0.40
≥ 60	47	-1.7 (-7.4, 4.1)	

-20 -10 0 10 20

Treatment difference (mmHg)

p-values not adjusted for multiplicity

Reduction in 24-hour SBP generally consistent across subgroups

HTN-OFF Subgroup Analysis – Full Cohort

Plasma Renin Activity

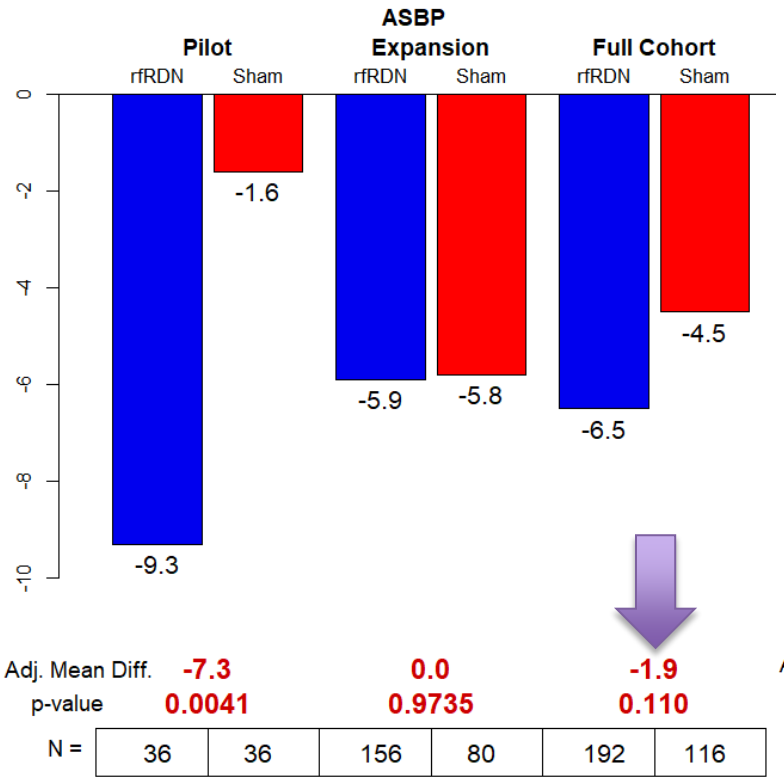
Plasma Renin Activity			
Plasma Renin Activity	**# of Patients**	**Treatment difference**	**Interaction p value**
<0.65	138	-1.51 (-4.79, 1.76)	0.09
≥0.65	137	-5.49 (-8.72,-2.26)	

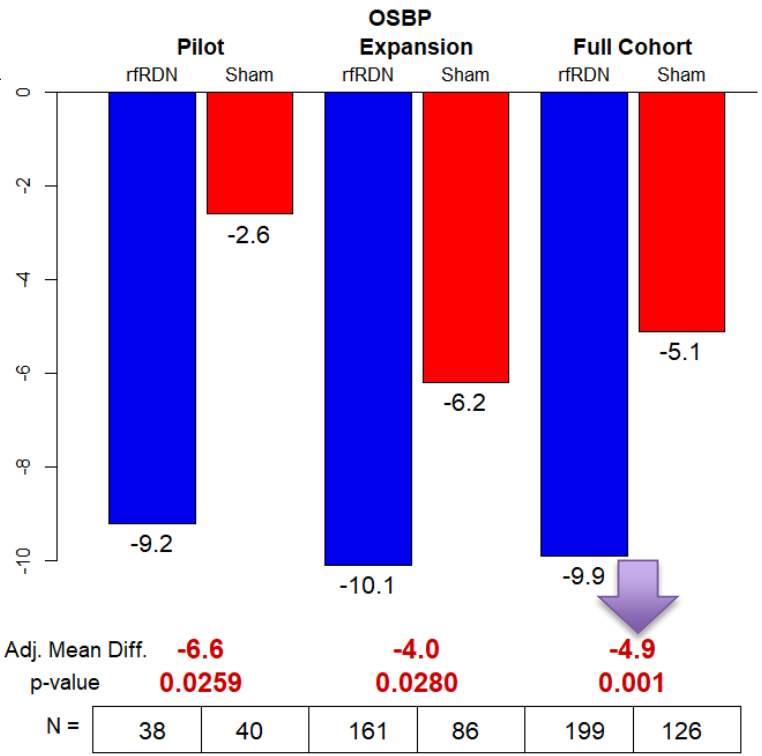
p-values not adjusted for multiplicity

HTN-ON EFFECTIVENESS RESULTS

HTN-ON ASBP & OSBP Results at 6 Months

Pilot, Expansion, and Full Cohort Frequentist Analysis





p-values not adjusted for multiplicity. SBP changes are unadjusted reductions from baseline

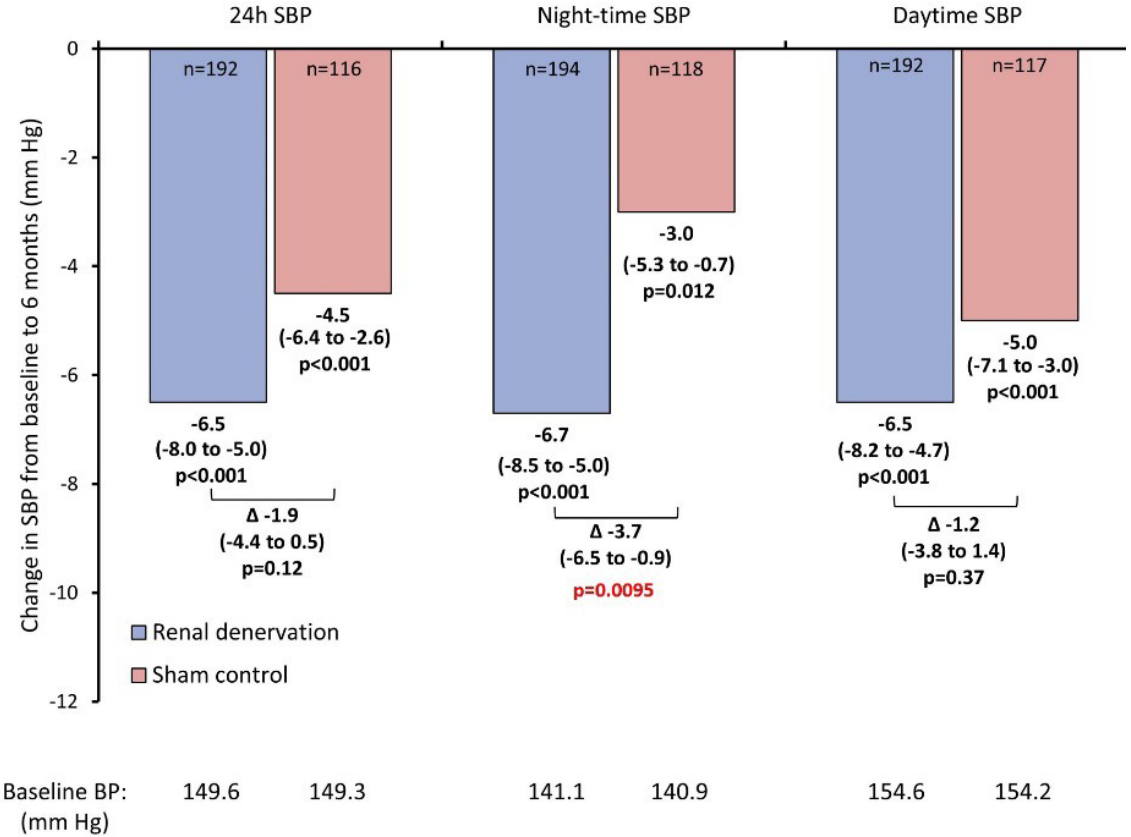
Differences and p-values determined from ANCOVA models adjusting for the baseline value

HTN-ON Primary and Secondary Effectiveness Endpoint
Bayesian Analysis

	Pilot Cohort sample size (evaluable)	Effective Pilot Cohort sample size after discounting	α-discount parameter estimate	Expansion Cohort sample size	Bayesian estimate of treatment effect (95% BCI)	Posterior probability of success (>0.975 meets success criteria)
Primary Endpoint: 24-hour ASBP @ 6 months						
rfRDN	36	6.999	0.194	156	-0.03 mmHg (-2.8 to -2.8)	0.508
Sham	36	0.007	0.0002	80		
Secondary Endpoint: Office SBP @6 months						
rfRDN	38	38	>0.999	161	-4.1 mmHg (-7.4 to 0.75)	0.992
Sham	40	6.2	0.156	86		

HTN-ON Daytime vs. Nighttime ASBP at 6 Months

Full Cohort



p-values not adjusted for multiplicity. SBP changes are unadjusted reductions from baseline
Differences and p-values determined from ANCOVA models adjusting for the baseline value

HTN-ON Nighttime ASBP 6 Months

12 AM (midnight) to 6 AM

	Adjusted Treatment Difference (95% CI) Between rfRDN and Sham Groups from Baseline to 6 months	p-value
Full Cohort	-3.09 (-5.91, -0.26)	0.032
Pilot	-8.4 (-14.4, -2.4)	0.007
Expansion Cohort	-0.7 (-3.9, 2.5)	0.656

p-values not adjusted for multiplicity

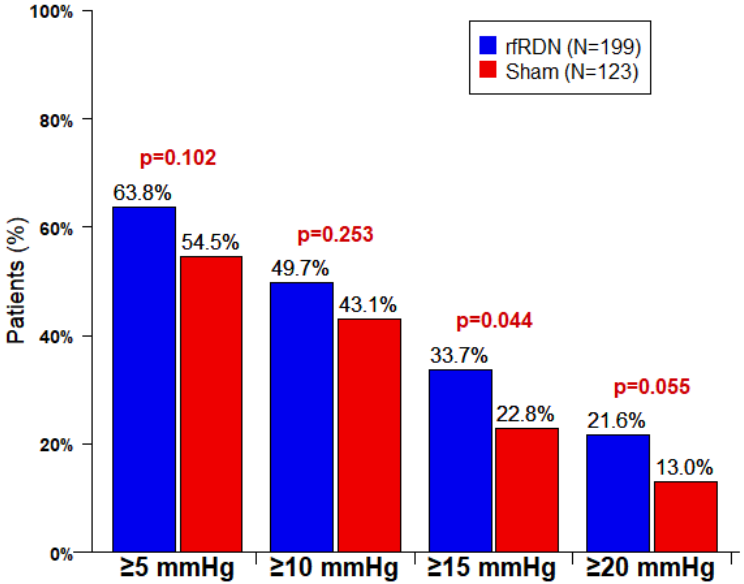
Results of HTN-ON Full cohorts are not adjusted for differences in randomization ratios

Differences and p-values determined from ANCOVA models adjusting for the baseline value

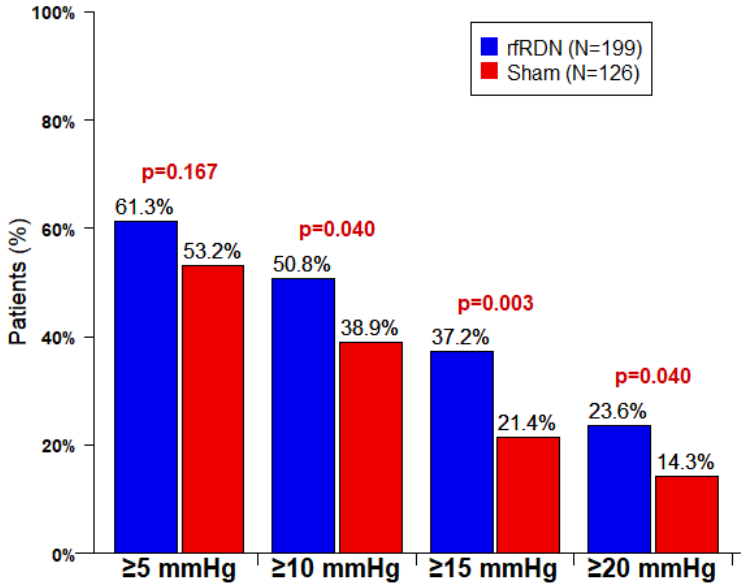
HTN-ON Office SBP Changes at 3 and 6 Months

Full Cohort

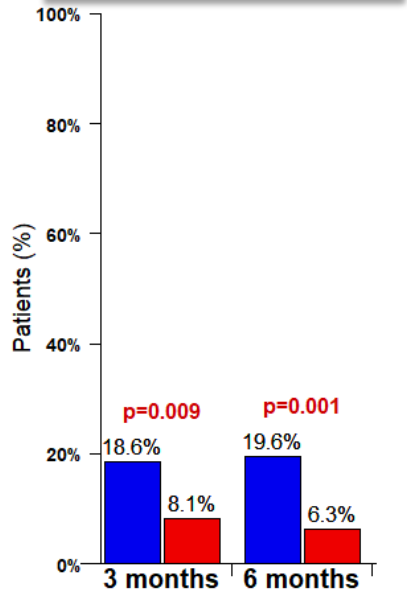
OSBP at 3 months



OSBP at 6 months



Subjects at target (<140 mmHg)



p-values not adjusted for multiplicity

HTN-ON Potential Confounders Affecting the Primary 24-Hour ASBP Endpoint

- Sham group increased medications more than RDN group
- Missing ABPMs may have impacted the effectiveness results

HTN-ON Medication Burden

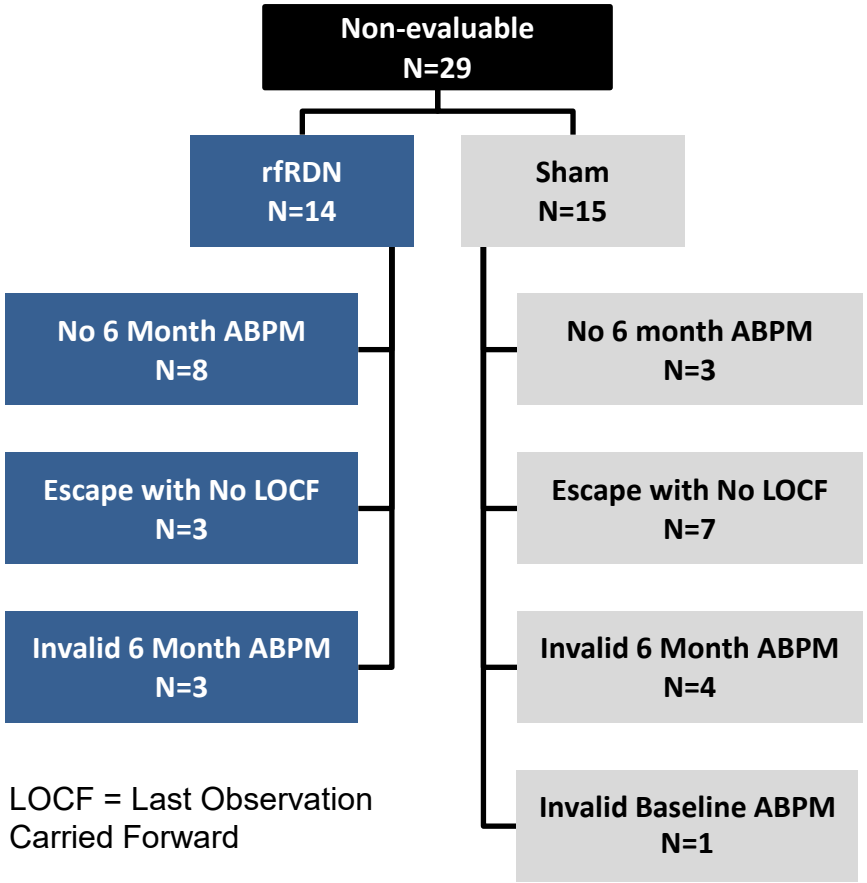
Full Cohort

MEDICATION INDEX 1 ANTIHYPERTENSIVE LOAD INDEX						
	rfRDN (n = 206)	Change from baseline (unadjusted)	Sham (n = 131)	Change from baseline (unadjusted)	p-value	Difference in Changes
Baseline	1.20 ± 0.85	0	1.17 ±0.87	0	0.737	0
3 months follow-up	1.22 ± 0.89	0.02	1.26 ± 0.86	-0.09	0.150	-0.07
6 months follow-up	1.25 ± 0.88	0.05	1.34 ± 0.83	-0.17	0.073	-0.12

p-values not adjusted for multiplicity

HTN-ON: Missing 6 Month ABPM Data

Full Cohort



LOCF = Last Observation Carried Forward

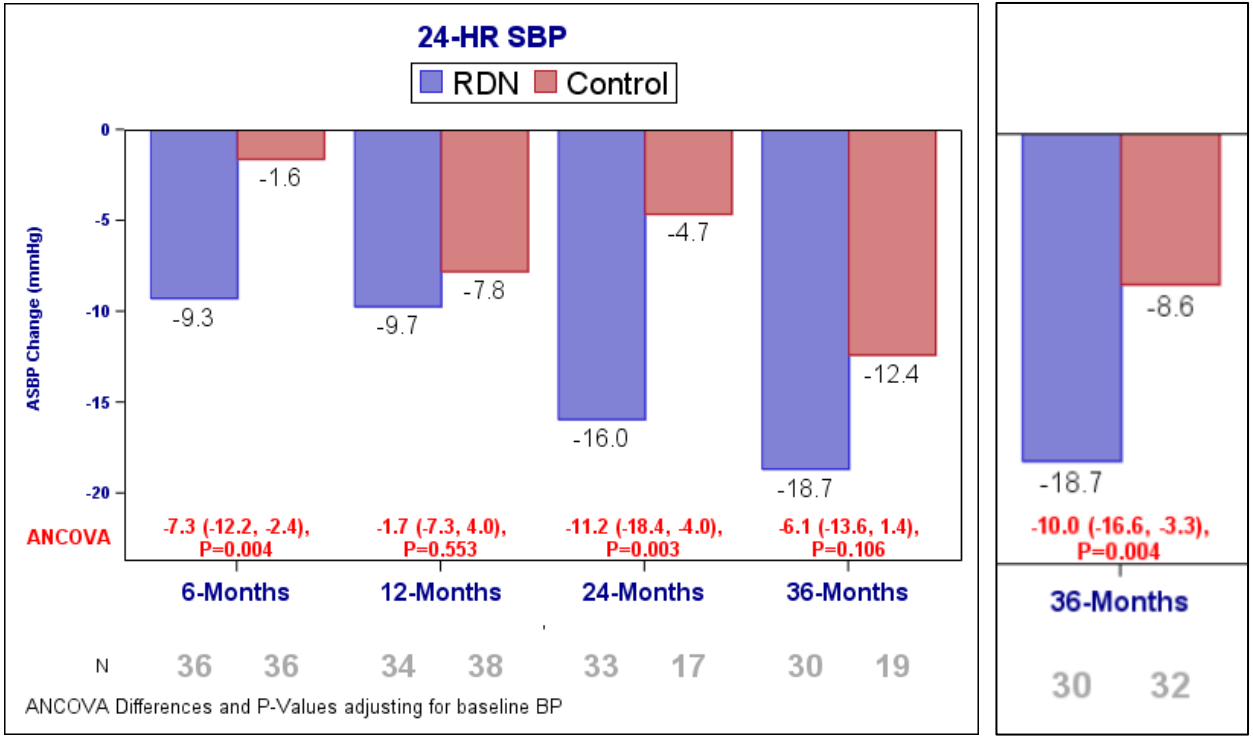
Randomization

- Pilot 1:1
- Expansion
  - First 26 subjects – 1:1
  - Remaining 231 subjects – 2:1 (rfRDN:Sham)

Missing Data

- rfRDN: 14/206 (6.8%)
- Sham: 15/131 (11.5%)

HTN-ON BP Reduction Durability – Pilot Cohort



Without data imputation

With data imputation[12]

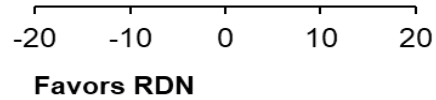
Subject unblinding at 12 months

p-values not adjusted for multiplicity

12. Mahfoud ea. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet. 2022;399(10333):1401-1410.

HTN-ON Subgroup Analysis at 6 Months – Full Cohort

Subgroup		RDN N	Sham N	24-h ambulatory systolic BP adjusted treatment difference mmHg (95% CI)	interaction p-value
Age	< 65	163	98		**0.99**
	≥ 65	29	18		
Sex	Male	157	88		**0.84**
	Female	35	28		
BMI	Tertile 1 (<28.9)	72	30		**0.66**
	Tertile 2 (28.9 to 33.1)	62	41		
	Tertile 3 (≥33.1)	58	45		
Type II Diabetes	Yes	21	19		**0.28**
	No	171	97		
Smoking Status	Current	28	19		**0.29**
	Former	68	36		
	Never	96	61		
Baseline eGFR(mL/min/1.73 m²)	<60	13	10		**0.38**
	≥ 60	179	106		
Obstructive Sleep Apnea	Yes	22	19		**0.10**
	No	170	97		
Geography	US	87	54		**0.011**
	OUS	105	62		
US Patients	Black Americans	31	15		**0.21**
	Non-Black Americans	56	39		
OUS location	Europe	78	46		**0.37**
	Japan	13	7		
	Australia	14	9		

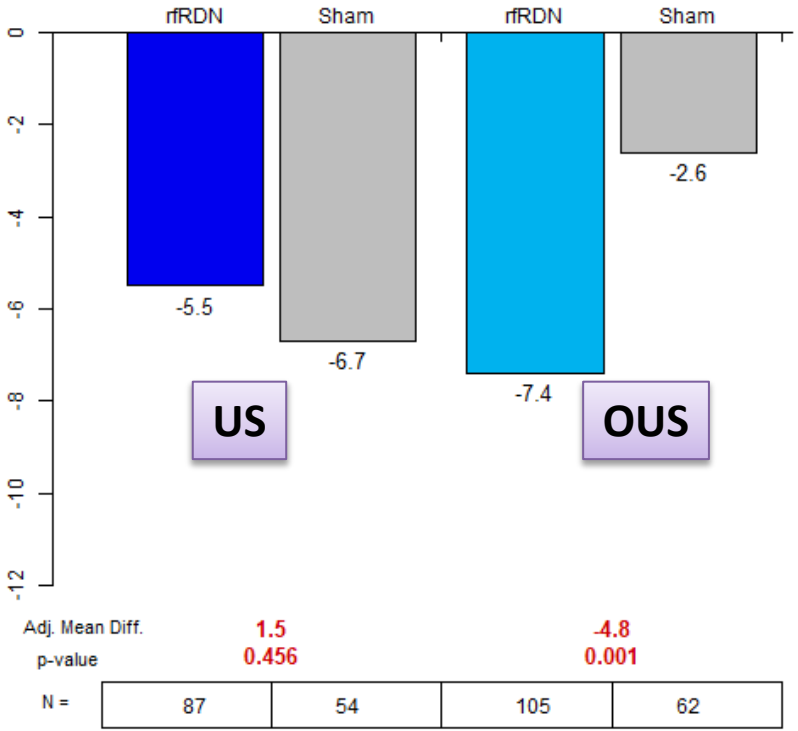


p-values not adjusted for multiplicity

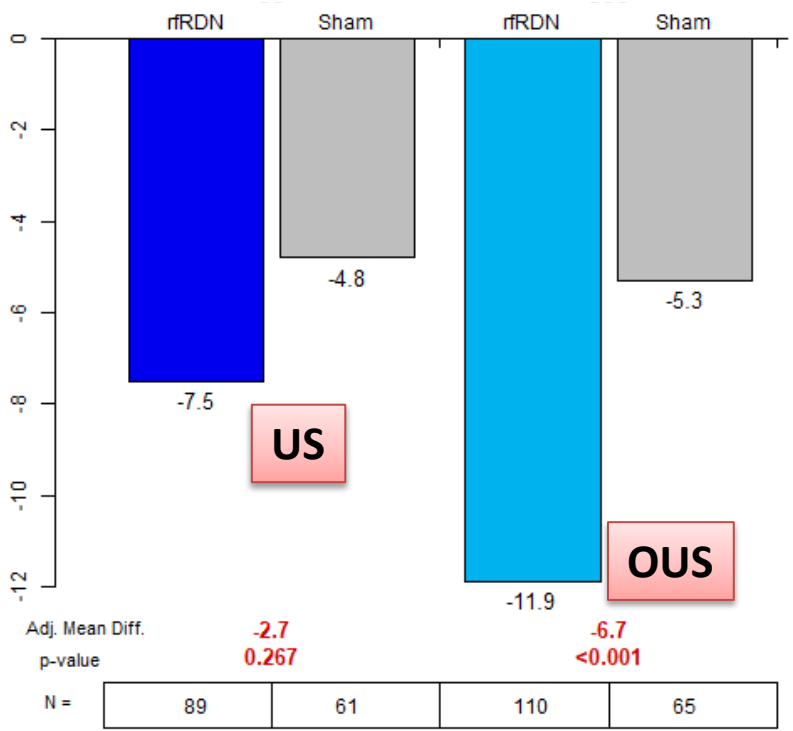
HTN-ON Subgroup Analyses at 6 Months – Full Cohort

ASBP and OSBP in US vs OUS Subjects

24-Hour SBP @ 6M



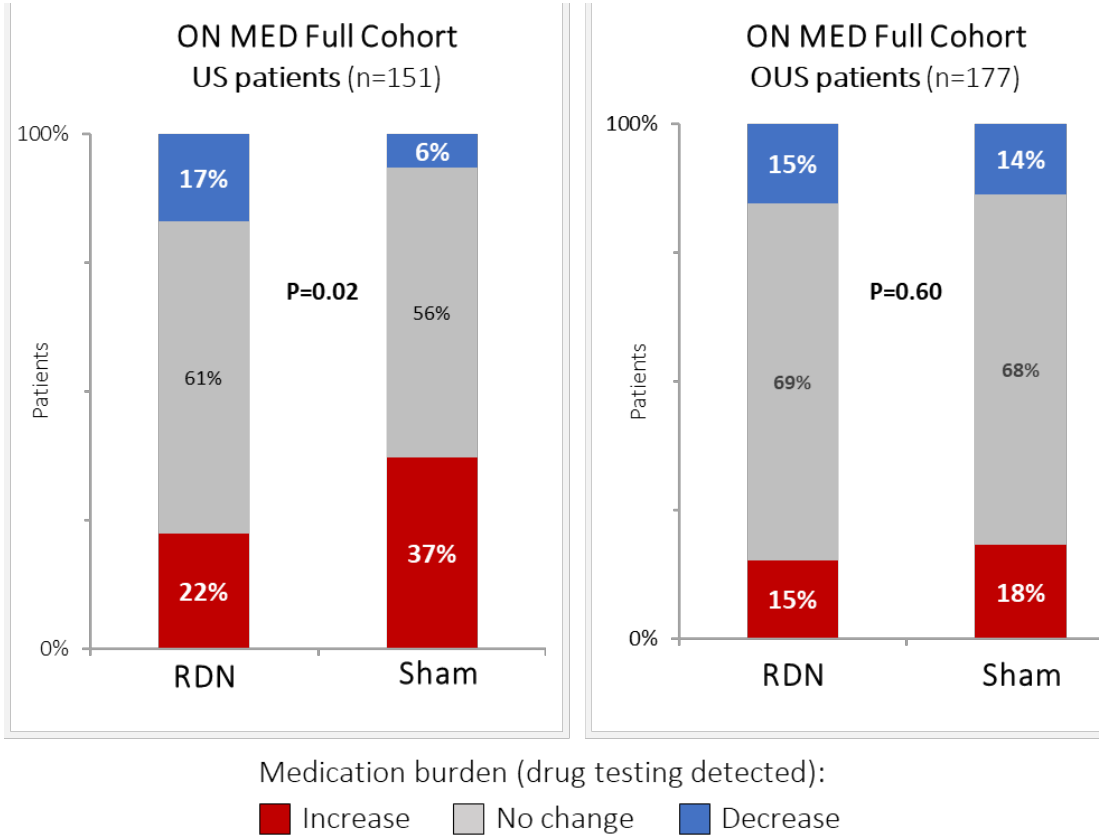
Office SBP @ 6M



p-values not adjusted for multiplicity

HTN-ON Subgroup Analysis at 6 Months – Full Cohort

Changes in Medication Burden in US vs. OUS Subjects



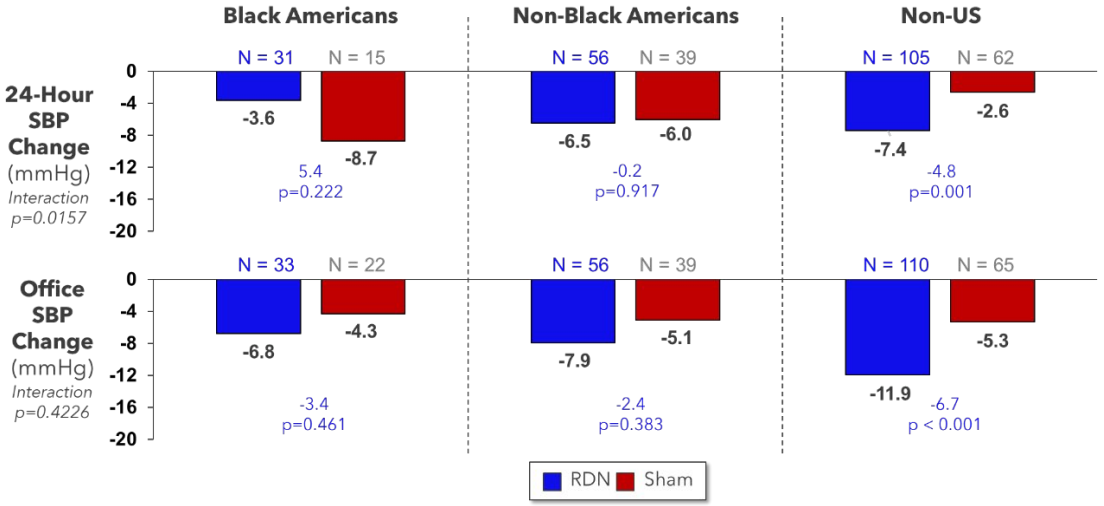
US: On average, Sham patients increased medications by 0.24 of a full med dose vs. rfRDN patients

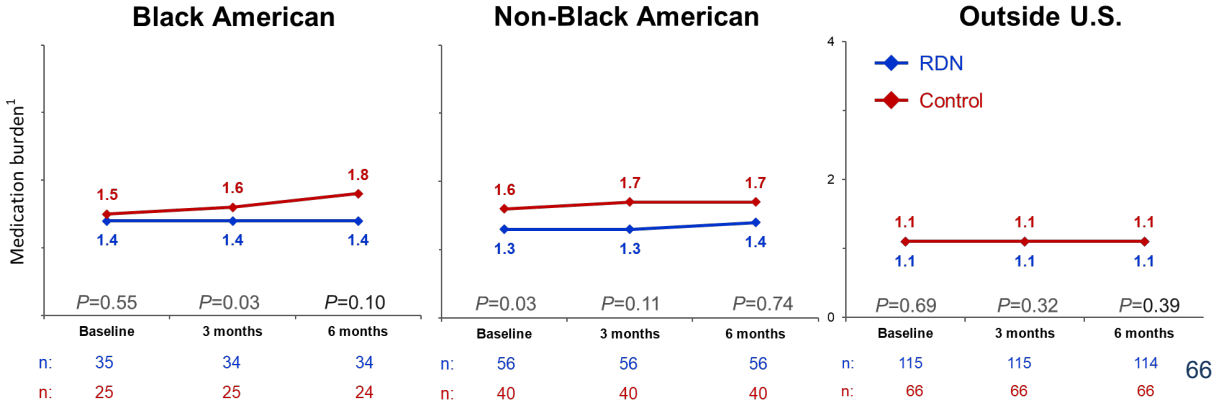
OUS: Sham and rfRDN subjects had similar medication change profiles

p-values not adjusted for multiplicity

HTN-ON Subgroup Analysis at 6 Months – Full Cohort

Black Americans vs. Non-Black Americans





p-values not adjusted for multiplicity

SAFETY RESULTS
HTN-OFF & HTN-ON

Primary Safety Endpoint

The primary safety endpoint was defined as the occurrence of at least one of the following major adverse events (MAE):

a. 30 days

- All-cause mortality
- End stage renal disease
- Significant embolic events resulting in end-organ damage
- Renal artery perforation requiring intervention
- Renal artery dissection requiring intervention
- Major vascular complications
- Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol

b. New renal artery stenosis (RAS), defined as a >70% stenosis, confirmed by renal angiography at 6 months as determined by angiographic core laboratory

Primary Safety Endpoint Results – All Subjects

Pooled analysis of the composite 30-day MAE rate and 6 months renal artery stenosis for evaluable rfRDN-treated subjects from HTN-OFF and HTN-ON

	n/N	Composite MAE Rate	95% CI	Performance Goal (PG)	p-value
First 253 evaluable subjects	1/253	0.4%	0, 1.9%	7.1%	<0.001
All subjects (pooled studies)	2/537	0.4%	0, 1.2%		

2 MAEs: Both femoral pseudoaneurysms

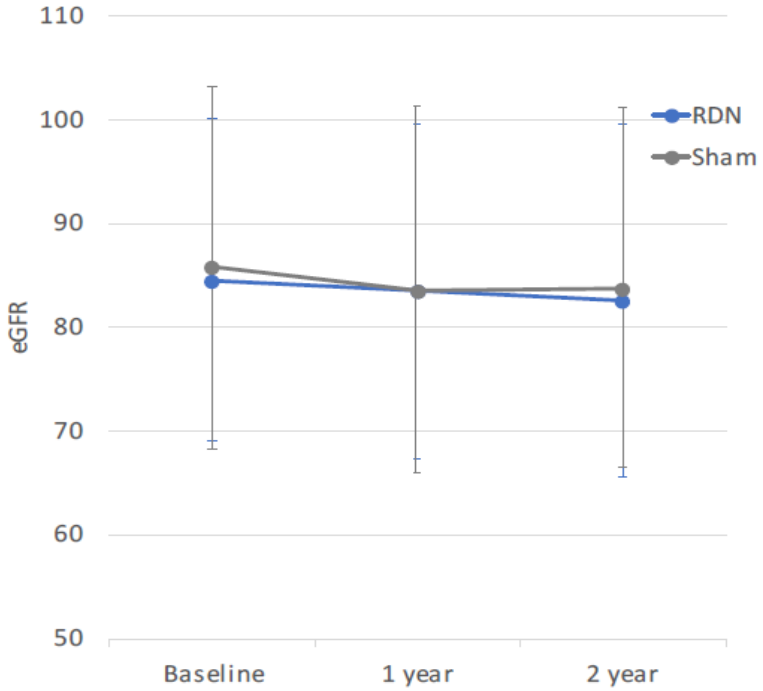
Renal Artery Stenosis Assessment
12 months CTA/MRA Study

- Pre-specified minimum of 150 subjects with diagnostic CTAs or MRAs at 12 months
- 206 patients with 12-month CTA or MRA
  - No subjects with a >70% diameter stenosis (DS) lesion confirmed by angiogram
  - 6 patients (2.9%) with potential >50% and ≤99% diameter stenosis (DS)
    - 4 subjects with no confirmatory imaging (CTA/MRA, angiogram)
    - 2 subjects with 60% stenosis by CTA
  - 2 patients with potential >50% and ≤99% DS had renal angiograms read by site as "no stenosis," but angiography was of insufficient quality for core lab to calculate DS

Incidence of new renal artery 50 to 99% DS by CT/MRA could be as high as 2.9% - 3.9%

HTN-OFF Full Cohort and HTN-ON Pilot

eGFR Through 2 Years



RDN	220	196	181
Sham	226	135	65

eGFR through 2 years similar between rfRDN and Sham

SUPPLEMENTARY CLINICAL DATA

Global SYMPLICITY Registry (GSR)

- Prospective, multi-center, single-arm, open label registry
- Enrolling up to 5000 subjects ≥18 years of age
  - Including broader patient population with more comorbidities vs. HTN-OFF and HTN-ON
- Follow-up through 60 months
- Device versions:
  - Symplicity Flex (single electrode, 1st generation device)
  - Symplicity Spyral (multi-electrode, current PMA device)

GSR 24-hour SBP Results

	Baseline	Change at 6-months	Change at 12-months	Change at 24-months	Change at 36-months
Symplicity Spyral Catheter	155.20 ± 20.10 N=542	-7.69 ± 18.72, N=289	-8.77 ± 18.04, N=242	-8.83 ± 17.96, N=132	-14.39 ± 21.93, N=74

Limitations of Registry Data

- Unblinded
- Single arm
- Unclear if drop in BP is due to RDN or to nonspecific placebo or Hawthorne effects or regression to the mean and the like
- In RDN trials, difference between unblinded HTN-2 (with reduction of SBP by 32 mmHg RDN over control) and sham controlled HTN-3 (2 mmHg difference) shows importance of sham controls

GSR Time in Target Range

- Time in Target Range (TTR) data presented for the GSR
- Caveats to consider
  - TTR is a measure of control of blood pressure. It is agnostic as to how BP control is achieved.
  - TTR not yet fully validated for clinical outcomes
  - Number of BP assessments (with interpolation) may be too few to accurately determine TTR
    - TTR literature often uses BP measurements spaced 1 or 3 months apart

Patient Preference Study

David Gebben, PhD
Health Economist
Office of Strategic Partnerships and Technology Innovation

Patient Preference Information (PPI)
CDRH Guidance

Guidance Document: *Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests and Inclusion in Decision Summaries and Device Labeling. August 2016*

- PPI Definition:

  qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions

  - Not a patient-reported outcome (PRO) or other clinical trial endpoint or outcome

Benefit-Risk Determination

- Before considering Benefit-Risk (B-R), establish reasonable assurance of safety and effectiveness
- CDRH recognizes the patient preference information can supplement the assessment of benefits and risks
- Patient preference studies consider how patients tradeoff the benefits and risks of treatment options[13]

13. FDA Guidance. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications Guidance for Industry and Food and Drug Administration Staff. August 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

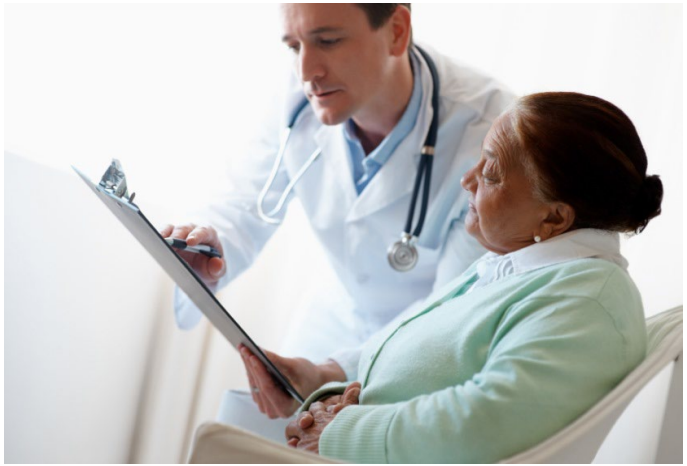
Recommended Qualities of Patient Preference Studies

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit. This may inform FDA's evaluation of a device's benefit-risk profile during the PMA, HDE application, and De Novo request review processes.

A. All about Patients
   - Patient Centeredness
   - Sample Representativeness
   - Capturing Heterogeneous Patient Preferences
   - Comprehension by Study Participants

B. Good Study Design
   - Established Good Research Practices
   - Effective Benefit-Risk Communication
   - Minimal Cognitive Bias
   - Relevance

C. Good Study Conduct and Analysis
   - Study Conduct
   - Logical Soundness
   - Robustness of Analysis of Results



14. FDA Guidance. Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Aug 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications

PPI Study Qualities

- 400 respondents to PPI Survey
- Qualities consistent with CDRH PPI Guidance:
  - Follows guidelines for good research practices established by recognized professional organizations
  - Followed good ethical research practices
  - Survey understandable to respondents
- Medtronic met with the FDA and incorporated feedback into the design of the study.

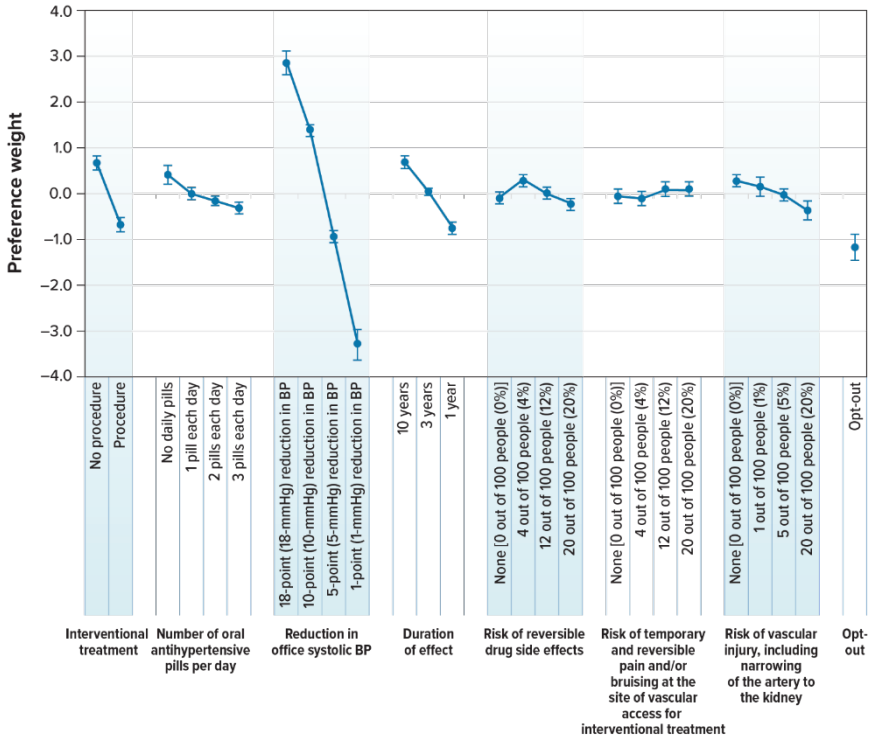
Treatment Feature	Treatment A	Treatment B
Minimally invasive surgical procedure to lower blood pressure	Procedure	No procedure
Number of daily pills to lower blood pressure	1 pill each day	2 pills each day
Reduction in systolic blood pressure measured in the doctor's office	10-point reduction in blood pressure	1-point reduction in blood pressure
How long the blood pressure reduction from the treatment lasts	1 year	1 year
Risk of drug side effects while taking blood pressure pills that may lead to more doctor visits	None (0 out of 100 people [0%])	20 out of 100 people (20%)
Risk of temporary and reversible pain and/or bruising in the upper thigh after the minimally invasive blood pressure procedure (up to 1 month)	12 out of 100 people (12%)	None (0 out of 100 people [0%])
Risk of injury to blood vessel requiring another surgery (likely minor) usually within 18 months	None (0 out of 100 people [0%])	None (0 out of 100 people [0%])

Example Choice Task

PPI Study Results by Attributes and Levels

- Results generally as expected with levels in order of expected preference
- Reduction in office systolic blood pressure was main driver of preference choices
- Risks of treatments were not as important

Results from patient preference study



PPI Study Results

- In general, patients accepted greater risks of side effects/adverse events from interventional treatment or pills for greater reductions in office systolic blood pressure
- From PPI survey results & possible B-R scenarios of treatment options, model of estimates for percentage of patients' treatment choices was created
- The scenarios suggest that between 15.1% - 30.9% of patients would select the RDN system intervention based on clinical scenarios

Post-Approval Study And FDA Conclusions

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Post Approval Study – AFFIRM

- Continued access protocol & post market study

Continued follow-up HTN-OFF & HTN-ON Subjects

Up to 200 rfRDN treated subjects

New Subjects

Up to 1000 new subjects
- OSBP ≥ 140 mmHg
- chronic kidney disease (CKD)
- isolated systolic HTN (ISH)
- type 2 diabetes mellitus (DM Type 2)

AFFIRM STUDY

Continued Follow-up Cohort

Additional 24 months follow-up after HTN-OFF/ON studies

60 months total follow-up post rfRDN

Main Cohort

Receive rfRDN on enrollment

36 months follow-up post rfRDN

Post Approval Study – AFFIRM Endpoints

- Safety: Incidence of MAE
- Effectiveness:
  - Change in OSBP, Home BP, 24hr ASBP
  - Procedural characteristics, BP medication burden, proportion requiring repeat RDN, and Time in Target Range
- Pre-specified subgroup analysis in ISH, CKD, DM Type 2 patients

Post Approval Study – General Considerations

- Training to facilitate procedural success with new users
- Further evaluation of patient subgroups (gender, race)
- Additional collection of long-term renal imaging
- BP reduction durability

FDA CONCLUSIONS

Conclusions (1)

- Primary safety endpoint met
  - Pooled safety rate of 0.4%
  - No new RAS cases (>70% diameter stenosis)
    - Potential rate <3.9% for 12 Month RAS >50% and < 99% DS
- HTN-OFF: Primary effectiveness endpoint met
  - Between-group difference in mean ASBP reduction of 3.9 mmHg in favor of RDN vs. Sham at 3 months
- HTN-ON: Primary effectiveness endpoint not met
  - Between-group difference in mean ASBP reduction of 0.03 mmHg at 6 months
  - Discordant results between the HTN-ON Pilot and Expansion cohorts
    - Multiple hypotheses proposed to help explain the potential reasons for the results

Conclusions (2)

- Strengths
  - Powered, randomized, sham-controlled, blinded trials
- Limitations
  - Small long-term RCT data sample size
  - Challenging interpretation BP reduction durability
    - Medication changes beyond 3 months (HTN-OFF) or 6 months (HTN-ON)
    - Longer-term BP measurements performed in unblinded subjects
    - Crossover from Sham to rfRDN reduced the sample size of the control group
- Patient Preference Study
  - Some patients may prefer rfRDN to an additional BP pill

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